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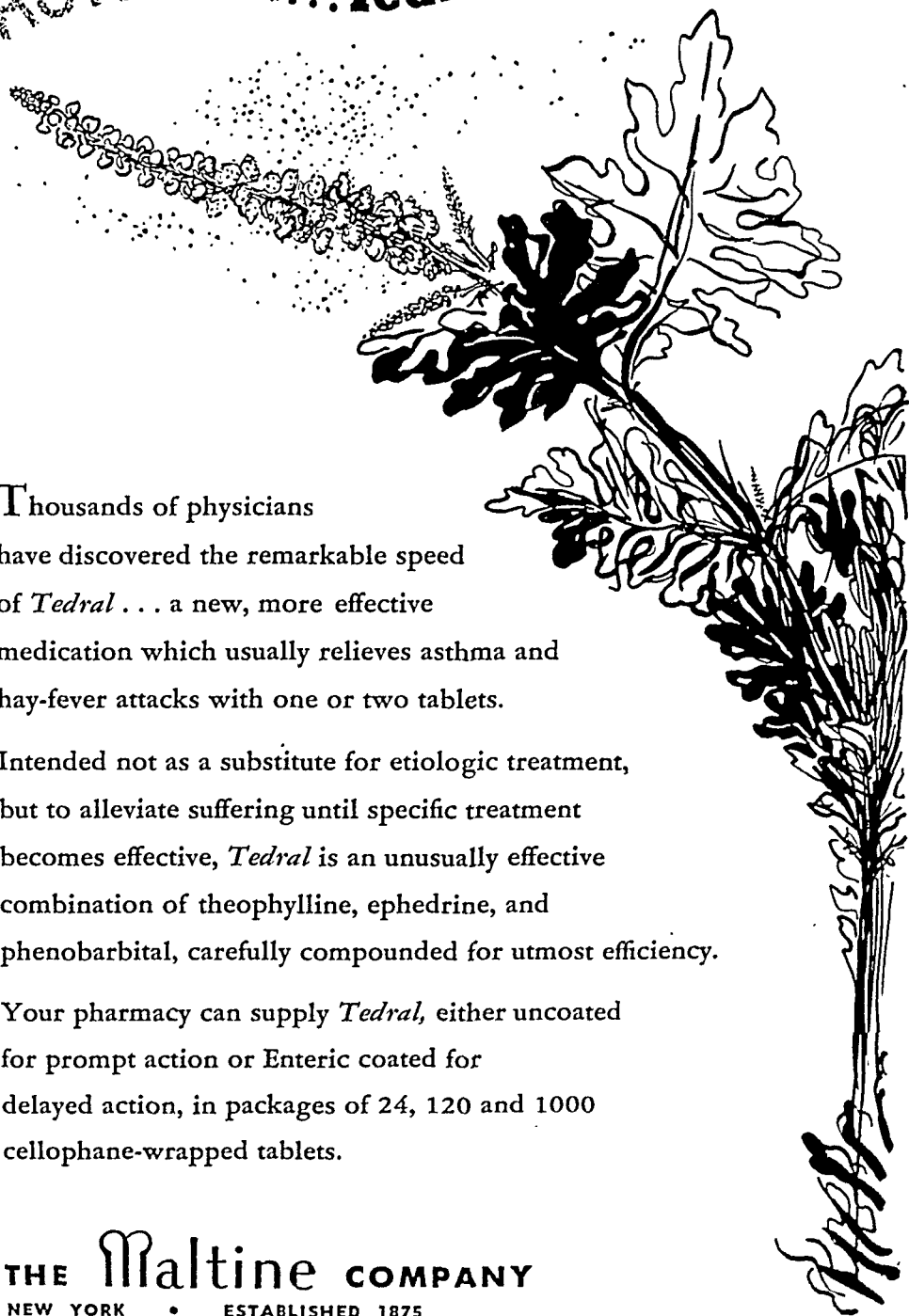
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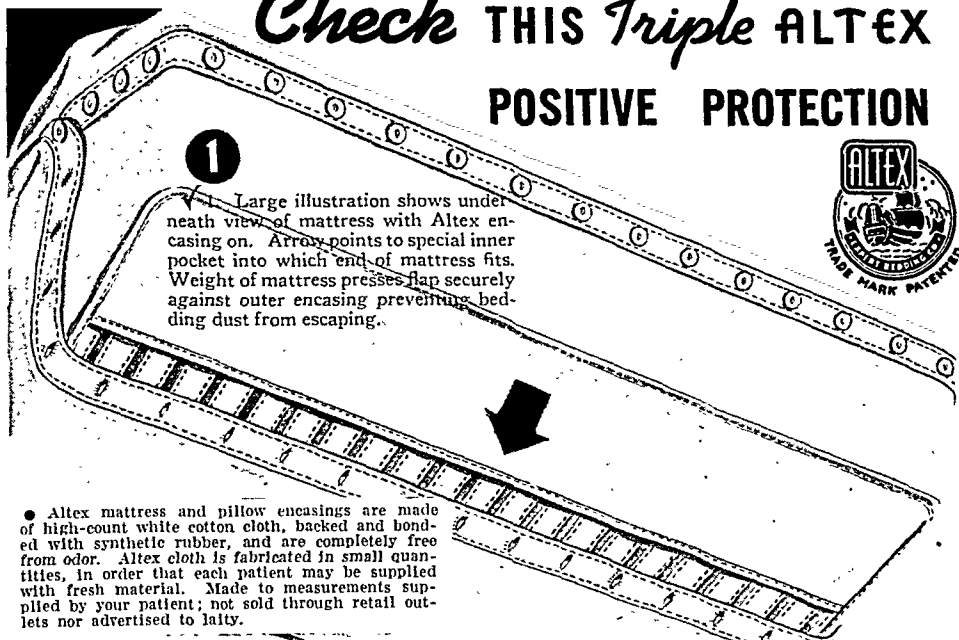
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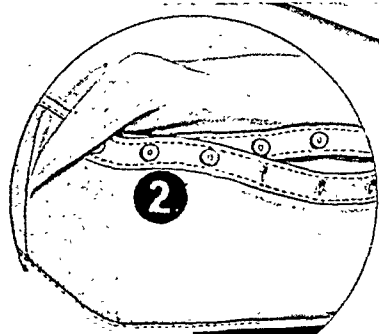
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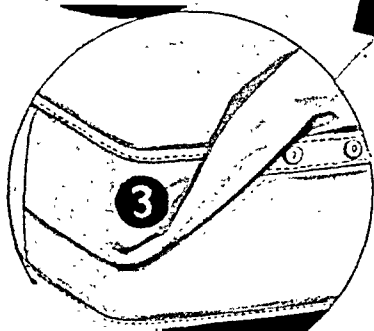
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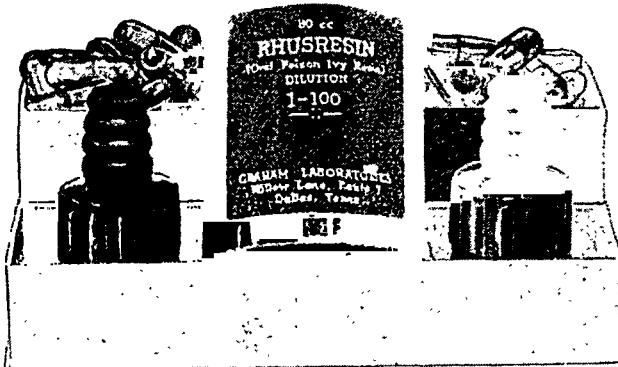
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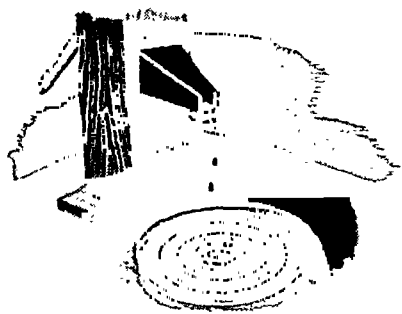
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## ALLERGIC PULMONARY CONSOLIDATIONS

O. C. HANSEN-PRUSS, M.D., F.A.C.A., and E. G. GOODMAN, M.D.\*

Durham, North Carolina

THE allergic response in the human frequently comprises symptoms referable to the respiratory tract. This response may range from a mild rhinitis to a severe reaction involving the entire pulmonary system. It seems, therefore, odd that striking pulmonary manifestations other than asthma were not recognized until Loeffler<sup>9</sup> reported them in 1932 and again in 1936. He described a symptom complex which he observed in patients with tuberculosis and which was characterized by the "sudden" appearance of extensive x-ray shadows in the pulmonary field. These x-ray shadows lasted at times only a few days. He stated that they resembled pneumonic infiltrations and that they were not usually accompanied by striking physical signs or symptoms. The appearance of the shadows was often related to a marked increase in the number of eosinophilic cells in the circulating blood. In one of his patients the eosinophil percentage was 66. According to his observations the symptom complex appeared almost exclusively during the summer months. Even though Loeffler first noted the condition in tuberculous patients and seemed impressed by the relationship of this syndrome of tuberculosis, only thirty-seven of his fifty-one patients were given a tuberculin test and in almost 50 per cent of these patients the tuberculin test was negative.

Since Loeffler's original description of the disease picture, many observers have reported a varying number of patients exhibiting the same clinical syndrome. The resulting picture has been often called Loeffler's syndrome or some other deceptive name. We have chosen the term allergic "consolidation" because there is no histopathological evidence to warrant the assumption that we are dealing with an inflammatory or infiltrative process. All we can say is that the pulmonary reaction leads to the formation of shadows which are recognized by roentgenograms.

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\*From the Department of Medicine, Duke University Medical School, Durham, N. C.



The scope of this paper does not permit a complete review of the literature which may pertain to this syndrome. We have selected a few reports which illustrate different clinical and pathological variations of this clinical complex.

In 1941 Bass<sup>2</sup> reported three children showing a general lymph node enlargement, leukocytosis, and extreme eosinophilia. Râles were heard throughout the chests and the breathing was described as asthmatic. In the second patient roentgenograms of the chest showed "fine pin-head shadows scattered throughout the lung." This second patient had a bone marrow biopsy which showed a white blood count of 160,000 with an eosinophil count of 20 per cent. The other two patients did not show pulmonary infiltrations. Of the three cases, two, including the one with the high bone marrow white count, recovered completely. He felt that the children did not have a truly allergic reaction but some disturbance of the blood-forming organs which simulated "eosinophilic leukemia." This report is mentioned because it emphasizes one feature of this allergic pneumonic response, namely, the extreme eosinophilia.

Wharton Smith and Alexander<sup>11</sup> in 1939 reported a child who showed a transitory type of pulmonary infiltration accompanied by leukocytosis and eosinophilia (39 per cent). The child was acutely ill, had a high irregular fever which was often spiking in character. However, the leukocyte count gradually fell and this was accompanied by progressive anemia. Finally, the child developed a beta hemolytic streptococcus septicemia which was heralded by a transitory leukocytosis (45,600) with 97 per cent lymphocytes) followed by a progressive leukopenia and agranulocytosis. Since the child received sulfonilamide, it is questionable whether the leukopenia was the result of this therapy. Autopsy showed a marked hyperplasia of the bone marrow but the majority of the cells were "either large or small lymphocytes and it was impossible to differentiate myeloblasts and lymphoblasts." They felt that this was an instance of fatal Loeffler's syndrome although "it seems likely that she had a leukemia." These authors, however, made a pertinent observation which will be discussed again, namely, that the "pulmonary infiltrations may occur in many conditions and may be due to various causes."

Elsom and Ingelfinger,<sup>6</sup> in 1942, described two patients who presented a picture of fever, pneumonitis, eosinophilia and an immune response to *Brucella abortus*. Both recovered and the authors felt that the disease process was a manifestation of chronic Brucellosis.

Chafee, Ross and Gunn<sup>4</sup> in the same year described six patients with asthma who presented a varying degree of eosinophilia and leukocytosis. All six of these patients died. It should be noted that three of them received some morphine compound. It was their impression that at least two of the patients died of pneumonia and one of them from cardiac failure. At least one of his patients developed a moderate anemia. These authors were struck by the high eosinophil count in the bone marrow material which they obtained and considered it a "very rare condition."

## PULMONARY CONSOLIDATIONS—HANSEN-PRUSS AND GOODMAN

They also found an infiltration of the myocardium with eosinophils. It was their impression that there was nothing "to explain the amazingly high eosinophilia found in the marrow," and that "this finding of an eosinophilia in the bone marrow of asthmatic patients is unusual."

In 1943 Smith<sup>12</sup> reported one patient with a transitory pulmonary infiltration and emphasized the severity and chronicity of the asthmatic symptoms, transitory eosinophilia and the relatively afebrile course. He again called attention to the fact that the pulmonary x-ray shadows might be mistaken for tuberculosis, and that the prognosis might be false unless the allergic background is recognized.

During the past few years we have observed six patients with "allergic consolidation of the lung" which illustrate the various clinical features of the syndrome described first by Loeffler.

### CASE REPORTS

*Case 1.—A twenty-year-old white woman who had recurrent attacks of asthma for a period of twenty-one months. She developed the picture of suppurative bronchitis, x-ray evidence of a pneumonitis in the left upper lobe, leukocytosis and eosinophilia and improved after seventeen days in the hospital.*

B. D. No. B 9914. This young woman was first seen July 27, 1943, because of recurrent severe asthma of twenty-one months' duration. Her father had had asthma, contracted in late adult life, for many years. Five weeks prior to admission she had her first attack of asthma and had been continuously and severely asthmatic ever since. She had lost 20 pounds in weight. The usual remedies, such as subcutaneous adrenalin and intravenous aminophyllin, produced only slight temporary relief. Ten days prior to admission she developed a pleuritic pain in the left side of the chest; a course of sulfonamide was followed by considerable improvement. One day before admission she felt feverish and began to cough up increasing amounts of a mucopurulent sputum. Her throat became sore and her respiratory difficulty increased.

*Physical examination.*—Temperature 39.6° C.; pulse 100; respiration 24; blood pressure 112/76. The patient was pale, undernourished and in severe respiratory distress.

Nasal mucosa was pale, edematous and moist. Pharynx was hyperemic. There was moderate emphysema with diminished expansion bilaterally. Respirations were fast and shallow with considerable expiratory difficulty. Tactile fremitus was increased in an area around the region of the left scapula posteriorly; percussion note was dull in the right interscapular region. Numerous asthmatic wheezes were present throughout both lung fields, and there were many coarse bubbling, moist inspiratory râles at the angle of the left scapula and at the left base. Cardiac rate was rapid without other abnormalities.

*Clinical findings.*—Blood count is shown in Table I. Kahn and Kline tests were negative. Sputum was frothy containing a few purulent greenish-yellow masses; microscopically there were numerous gram-positive diplococci but no acid-fast organisms or fusio-spirochetes. Cultures of the sputum yielded alpha hemolytic streptococci, non-hemolytic staphylococcus albus, and citreus, a light growth of pneumococci in Avery's media; the latter couldn't be typed. Weltmann reaction was C.B. 5-1½. Roentgenogram of the chest (Fig. 1) showed an area of homog-

# PULMONARY CONSOLIDATIONS—HANSEN-PRUSS AND GOODMAN

TABLE I

DATE	W.B.C.	PER CENT EOSINOPHILS	REMARKS
7/27/43	20,950	20	Recurrent asthma—2 years. Staticus asthmaticus—5 weeks.
7/29/43	17,500	23	Physical signs and x-ray evidence of a bronchopneumonia. (Fig. 1).
7/31/43	9,850	36	On sulfadiazine—0.5 gm q 4 hr.
8/2/43	11,050	34	Afebrile after first day.
8/5/43	9,450	15	25-75 c.c. sputum daily. Sputum filled with eosinophils.
8/7/43			Skin tests to the extrinsic factors were nega- tive.
8/13/43			Discharged—improved. (Fig. 2).
9/6/43	14,680	8	Readmitted. Asthma, chest pain and cough —3 days. Pneumonitis left lower lung. (Fig. 3).
9/9/43	12,360	12	Afebrile—sulfadiazine—0.5 gm. q.i.d.
9/14/43	16,680	21	Severe asthmatic attacks daily.
9/20/43	18,040	42	Sulfadiazine discontinued. Constant dyspnea but improved.
9/23/43	14,050 91,000 (B.M.)	40 21 (6% Myelo. E.)	Afebrile.
9/27/43	16,320	36	Still requiring symptomatic treatment daily.
9/29/43	15,880	33	
10/1/43	18,400	26	T rise to 38°C.—Sulfadiazine started again.
10/6/43	17,000	23	Severe asthma.
10/19/43	13,280	16	
10/26/43	8,720	15	Discharged—improved. (Fig. 4).
11/30/43	11,900	29	Return visit—frequent colds and occasional wheezing. Chest plate showed lung fields to be clear.

B.M.—Bone marrow obtained by sternal aspiration.

Myelo—Myelocytes.

enous clouding in the left upper lung field with a suggestion of a cavity in the upper third; also a small amount of clouding in the first interspace anteriorly on the left. Other accessory findings were negative including a tuberculin test. The clinical impression was intrinsic asthma with a superimposed bronchopneumonia.

*Course in the hospital.*—The patient was given sulfadiazine, 0.5 grams every four hours for ten days. The temperature fell to normal twenty-four hours after admission and remained about 37 degrees C thereafter. During the first week the patient had severe asthmatic attacks nightly, necessitating intravenous aminophyllin, subcutaneous adrenalin, aminophyllin suppositories, and tablets of ephedrine sulphate, phenobarbital and aminophyllin for relief. She expectorated 25 to 50 c.c. daily; the material was at first purulent and later clear and mucoid. Repeated examinations of the sputum showed few bacteria but many eosinophils. She was discharged after seventeen days, improved. Roentgenogram of the chest (Fig. 2) on August 12 showed that the area in the left upper lobe had decreased considerably in size. The patient was skin tested to the various pollens, contacts, foods and fungi with negative results.

She was re-admitted on September 5, approximately three weeks after discharge.

# PULMONARY CONSOLIDATIONS—HANSEN-PRUSS AND GOODMAN

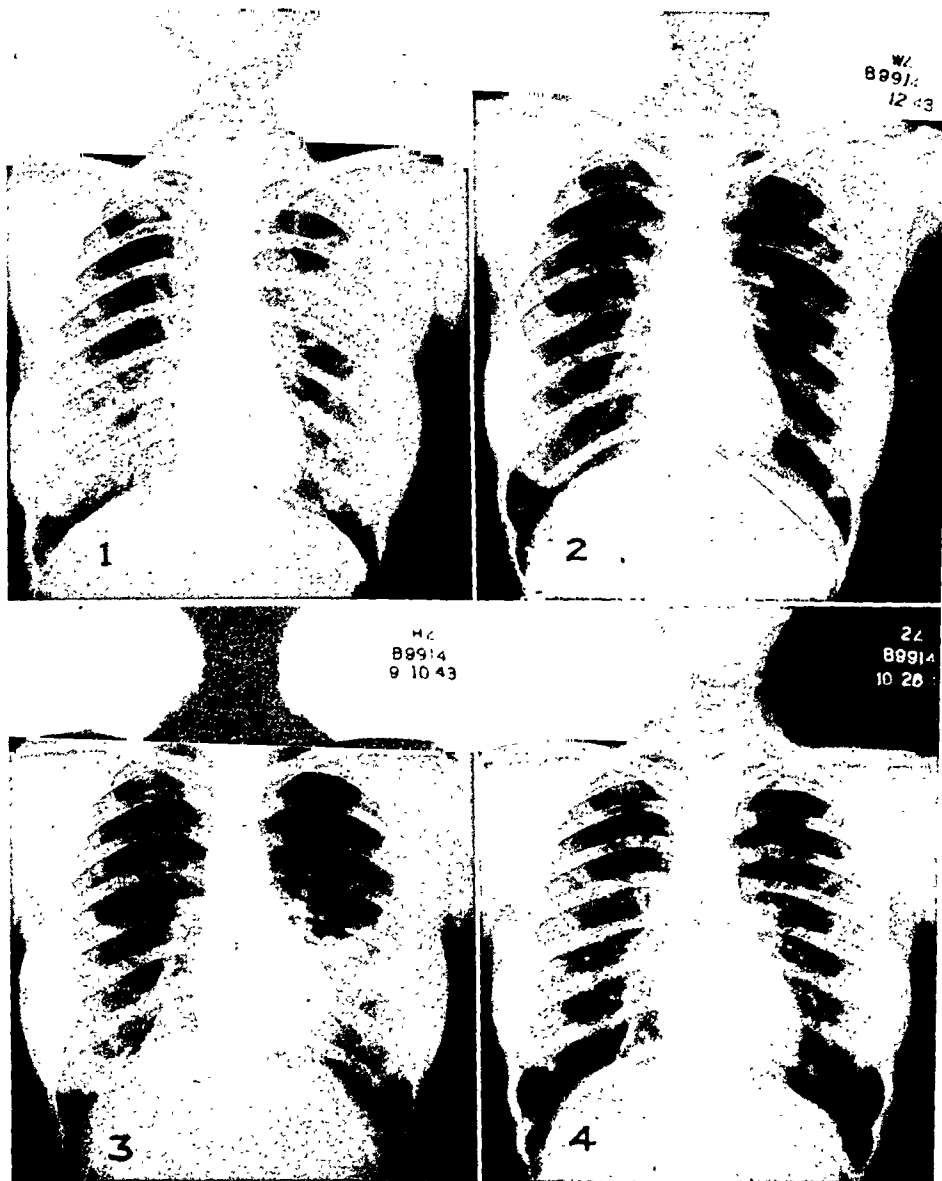


Fig. 1. (Case 1) Chest plate taken July 30, 1943, showing an area of homogenous clouding in the left upper lung field with a small amount of clouding in the first interspace anteriorly on the left. White blood count 17,500; eosinophils 23 per cent.

Fig. 2. (Case 1) Chest plate taken August 12, 1943, showing area in left upper lobe decreased considerably in size but still some residual clouding. White blood count 9,450; eosinophils 15 per cent.

Fig. 3. (Case 1) Chest plate taken September 10, 1943, showing the process in left upper lung to have completely disappeared but now an infiltration in the left lower lung field. White blood count 12,360; eosinophils 12 per cent.

Fig. 4. (Case 1) Chest plate taken October 26, 1943, showing the process in left lower lung to have largely disappeared. Both lungs are now clear. White blood count 8,720; eosinophils 15 per cent.

## PULMONARY CONSOLIDATIONS—HANSEN-PRUSS AND GOODMAN

TABLE II

DATE	W.B.C.	PER CENT EOSINOPHILS	REMARKS
1/20/32			Asthma, intrinsic—since childhood. Chronic T & A. Skin tests negative to extrinsic factors and autogenous vaccine.
2/2/32			Marked peribronchial thickening. Suspicious of bronchiectasis.
3/27/41			Blood streaked sputum for 2 weeks. X-ray suspicious of bronchiectasis (Fig. 5).
9/2/42	39,000	80	U.R.I. Afebrile and asthma. X-ray shows patchy infiltration in right lung. Suggestive of bronchopneumonia (Fig. 6).
9/4/42	63,000	82	X-ray unchanged. Afebrile. Subjectively well.
9/8/42	52,000 79,000 (B.M.)	83 45 (9% Myelo. E.)	Skin tests were negative to the extrinsic allergens.

The asthma had returned and she complained of chest pain and cough productive of varying amounts of sputum. These symptoms had been present for three days. Temperature on admission was 38.3. Tactile fremitus was increased over the left upper chest posteriorly and both lung fields were filled with musical râles. There was a moderate tachycardia. No other physical abnormalities were evident.

*Clinical Findings.*—For blood counts and bone marrow studies see Table I. Roentgenogram of the chest (Fig. 3) showed the disappearance of the shadow in the left upper lung field; there was now some clouding in the left lower lung field with several suspicious areas of rarefaction. Sputum examination disclosed a large number of eosinophils, otherwise nothing of significance. The electrocardiogram showed a shift of the pacemaker to A-V node in lead 2 and a moderate sinoauricular tachycardia. The patient was given sulfadiazine, 0.5 grams four times a day for ten days. Again she became afebrile soon after admission and remained so until discharge. She had asthma almost continuously despite various remedies, including a mixture of oxygen and helium. She gradually improved and was discharged seven weeks after admission. At this time the lung fields were fairly clear by x-ray (Fig. 4). White blood count was 8,720 with 15 per cent eosinophiles.

*Case 2.*—A twenty-two-year-old colored man; asthmatic since childhood; x-ray shadows suggestive of bronchiectasis at both lung bases; leukocytosis with eosinophilia and severe asthma.

C. H., No. 10,718. This young colored man was first admitted in January, 1932, complaining of asthma since childhood. One brother had asthma. His history suggested the intrinsic type of asthma brought on by frequent upper respiratory infections.

*Physical examination.*—The patient was well nourished and adequately developed; his tonsils were enlarged and chronically infected. There was moderate emphysema. Breath sounds were accompanied by musical râles. No cardiac abnormalities were noted and the rest of the physical examination was non-contributory. A roentgenogram of the chest showed generalized peri-bronchial thickening radiating from both hila; the thickening was especially marked about the lower bronchi, "suggestive of bronchiectasis." Skin tests to the common allergens and to an autogenous vaccine were negative.



Fig. 5. (Case 2) Chest plate taken March 27, 1941, showing peribronchial thickening, especially in lower lobes suggestive of bronchiectasis.

Fig. 6. (Case 2) Chest plate taken September 1, 1942, showing an increase in density around right hilum with extension upward toward the right apex suggesting a bronchopneumonia. White blood count 39,000; eosinophils 80 per cent.

In March, 1941, the patient returned complaining of a productive cough; the sputum had at times been blood streaked during the preceding two weeks. He had lost 10 pounds in weight. A week before admission the cough had become more harrassing and productive and he was expectorating about one cupful of a mucopurulent material daily.

*Physical examination.*—Temperature, pulse and respiration were normal. There was no evidence of sinus infection. The pharynx was reddened, and tonsils were enlarged. Musical râles were heard throughout the chest and moist inspiratory râles in both hilar regions. Heart was normal. Blood pressure was 114/80. Roentgenogram of the chest (Fig. 5) showed an increase in the peri-bronchial thickening in both lower lobes and some thickening of the right interlobar fissure. There were no tubercle bacilli or spirochetes in the sputum. The patient returned September 1, 1942, because of a recurrence of the asthma following an upper respiratory infection. Examination disclosed that the breath sounds were increased over the left anterior chest; there were moist and crepitant râles over the right lower chest anteriorly and the left lower chest posteriorly.

*Clinical Findings.*—White blood count was 39,000 with 80 per cent eosinophils (Table II). A chest plate showed a considerable increase in density around the right hilum extending towards the apex "suggesting a bronchopneumonia." There was a marked peri-bronchial thickening in both lung fields consistent with bronchiectasis (Fig. 6). Weltmann reaction was C.B. 5. Kahn and Kline tests were negative. The patient returned one week later feeling better. Skin tests to the various allergens including fungi were negative. Cultures of the sputum yielded pharyngis siccus, alpha hemolytic streptococcus, and anaërobic bacteria. Complete blood and bone marrow studies were done at this time (Table II).

TABLE III

DATE	W.B.C.	PER CENT EOSINOPHILS	REMARKS
10/15/40	16,500	51	Asthma—3 years. Athlete's foot—2 months. X-ray shows thickening around hila (Fig. 7). Severe dermatophytosis. Bilat. Caldwell-Luc and ethmoidectomy. Started desensitization. Afebrile.
10/18/40	22,050	19	
9/17/42	6,750	8	Recurrence of asthma following a cold.
1/21/43	24,000	8	Staticus asthmaticus—1 week. Mottled consolidation in both mid lungs (Fig. 8).
1/27/43	17,800	35	Severe asthma. Chest filled with coarse and fine moist râles.
1/29/43	21,000	16	Staticus asthmaticus continues.
2/8/43	22,000	24	Improving.
2/11/43	28,000	39	
2/16/43	13,000	59	Chest clear. Asymptomatic
2/17/43	11,000 121,000 (B.M.)	47 7 (17% Myelo. E.)	Discharged.
4/9/43	6,800 53,000 (B.M.)	18 5	Return visit. Greatly improved. Chest plate taken (Fig. 9).

*Case 3.*—A thirty-five-year-old white woman who gave a history of asthma of four years' duration and a negative family history for allergy. In the fourth year of her asthma she developed severe bronchospasm and x-ray signs of consolidation in both mid-lungs accompanied by leukocytosis and eosinophilia without fever.

J. W. No. A 49242. This patient was first seen October 15, 1940, giving a history of asthma of four years' duration. Family history was negative for allergy. Asthmatic symptoms were preceded by recurrent nasal obstruction, sneezing and rhinorrhea, the first attack of asthma occurring one year later, soon after an operation on the nose. The nasal symptoms were most pronounced in the spring and fall, whereas the asthma was usually precipitated by upper respiratory infections.

*Physical examination.*—The patient was well developed and nourished, but coughed and wheezed considerably. She had moderate seborrhea and acne of the face, shoulders, and trunk. Nasal mucosa was pale, and there was no nasal discharge. The right antrum was cloudy. Tonsils were hyperemic and ragged. There was slight emphysema. Constant inspiratory musical râles could be heard throughout and coarse inspiratory râles at the left base. Heart was normal. The rest of the physical examination was non-contributory except for moderate dermatophytosis about the left great toe.

*Clinical findings.*—Hemoglobin and red blood count were normal. White blood count was 15,500 with 51 per cent eosinophils (Table III). Kahn and Kline tests were negative. Roentgenogram of the sinuses showed densely thickened membranes of the antra and ethmoids. Roentgenogram of the chest showed bronchial thickening about both hila, particularly on the left side, and deformity of both diaphragms (Fig. 7). Sputum culture yielded alpha streptococci, staphylococcus aureus, and anaërobic bacteria. Skin tests to common allergens gave positive reactions to dust, a few pollens and molds. The clinical impression was a mixed type of asthma and chronic maxillary sinusitis. The patient entered the hospital and had a bilateral Caldwell Luc and ethmoidectomy. After discharge she was given a series of autogenous vaccine treatments with marked improvement.

She returned two years later because of a recurrence of severe asthma, having

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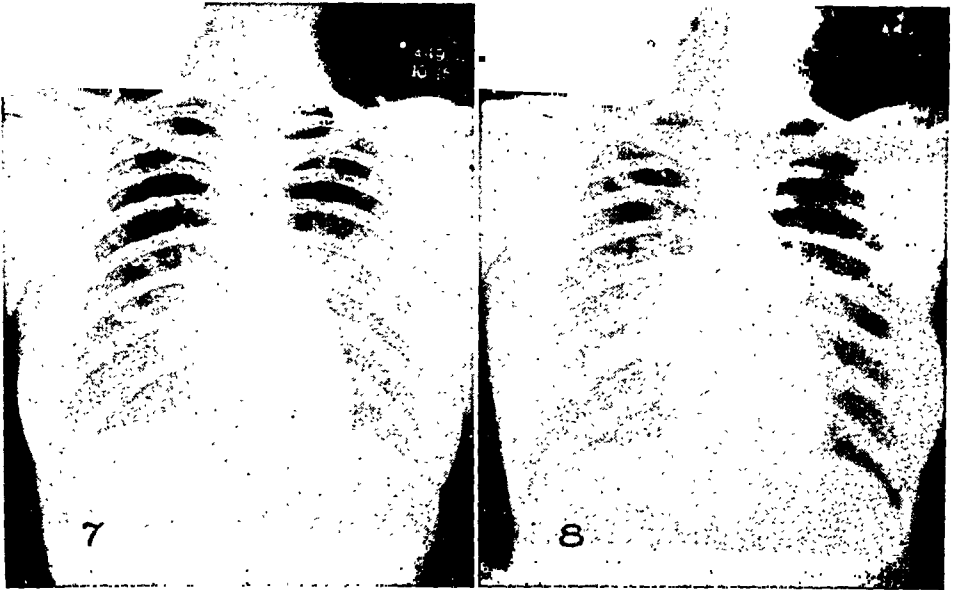


Fig. 7. (Case 3) Chest plate taken October 15, 1940, showing generalized peribronchial thickening at both hila, especially the left. Diaphragms are deformed by adhesions. White blood count 16,500; eosinophils 51 per cent.

Fig. 8 (Case 3) Chest plate taken February 10, 1943, showing mottled consolidation in both mid lungs. White blood count 28,000; eosinophils 39 per cent.

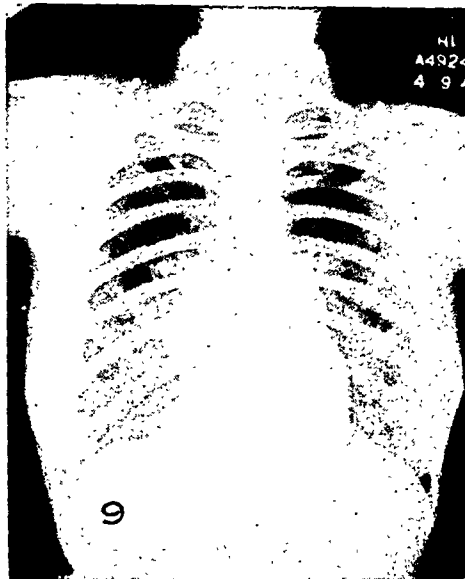


Fig. 9. (Case 3) Chest plate taken April 9, 1943, showing bronchial thickening in the lower lobes but no definite infiltration. White blood count 6,800; eosinophils 18 per cent.

stopped her autogenous vaccine treatments in the fall of 1941 soon after the birth of her baby. She had got along very well until two weeks before re-admission when she developed a fresh upper respiratory infection. This was accompanied by severe paroxysmal cough, productive of whitish mucus and severe nocturnal asthma.



TABLE IV

DATE	W.B.C.	PER CENT EOSINOPHILS	REMARKS
8/15/42	66,000	59	Asthma—3 weeks. Numerous musical râles. X-ray shows increased hilar markings. (Fig. 10).
8/25/42	56,560 120,700 (B.M.)	71 42 (9% Myelo. E.)	Feeling well. Skin tests to extrinsic allergens were negative. Low-grade fever. 37.5°C.
9/14/43	57,000	69	Report from L.M.D. Child passed round worm.
10/20/43	64,000 142,400 (B.M.)	64 33	Marked thickening around right hilum. Soft infiltration in lung field suggestive of tbc. Asymptomatic except for nocturnal cough. (Fig. 11).
4/6/43	19,000 110,000 (B.M.)	24 14 (2% Myelo. E.)	Looking well, feeling well. Some cough. Has been dewormed.
7/6/43	10,450 74,000 (B.M.)	14 15 (3% Myelo. E.)	(Fig. 12). Asymptomatic. Examination essentially negative.

The important physical findings were inspiratory and expiratory musical râles throughout both lung fields.

*Clinical findings.*—Hemoglobin and red blood count were within normal limits; white blood count normal; eosinophils 8 per cent. Roentgenogram of the chest showed essentially the same findings previously described. Skin tests gave mild positive reactions to giant and short ragweed, river birch, white oak, dogwood, box elder, dust, orris root and rabbit epidermis. The patient was again started on autogenous vaccine treatments. She returned three months later because of severe asthma. At this time the chest was filled with asthmatic râles.

White blood count was 24,000, eosinophiles 8 per cent. The chest plate disclosed a mottled consolidation throughout both lung fields (Fig. 8). The clinical impression was that she had asthma with superimposed bronchopneumonia, probably of virus origin.

Sputum culture revealed alpha hemolytic streptococci, diphtheroids, *N. siccus* and anaërobic bacteria. No tubercle bacilli or pneumococci were obtained. The patient was skin-tested to all of the vaccines prepared from these organisms with negative results. Weltmann reaction was C. B. 4. She had a persistent tachycardia and severe asthma for a period of two weeks, refractory to the usual methods of treatment. She was given sulfadiazine without definite improvement. Bone marrow studies were done (Table III). She improved gradually and was discharged after thirty-two days in the hospital. Roentgenogram of the chest at this time showed a decrease in the consolidation in the left mid lung. The patient returned April 9, 1943, feeling quite well. Roentgenogram of the chest at this time disclosed bronchial thickening in the lower lobe but nothing to suggest tuberculosis. "A diffuse process with this clearing might suggest sarcoid" (Fig. 9). The white count was normal but the eosinophilia persisted. A tuberculin test was negative.

*Case 4.*—A one-year-old white boy with asthma of three weeks' duration, showing a marked leukocytosis and eosinophilia. Roentgenogram of the chest showed increased peri-hilar markings without infiltration (Fig. 10). Practically afebrile course.

B. H. No. A 89851. This boy was admitted to the hospital August 8, 1942, with asthma of three weeks' duration. The grandparents were asthmatic. Two weeks before admission the child developed a slight fever without signs of a marked

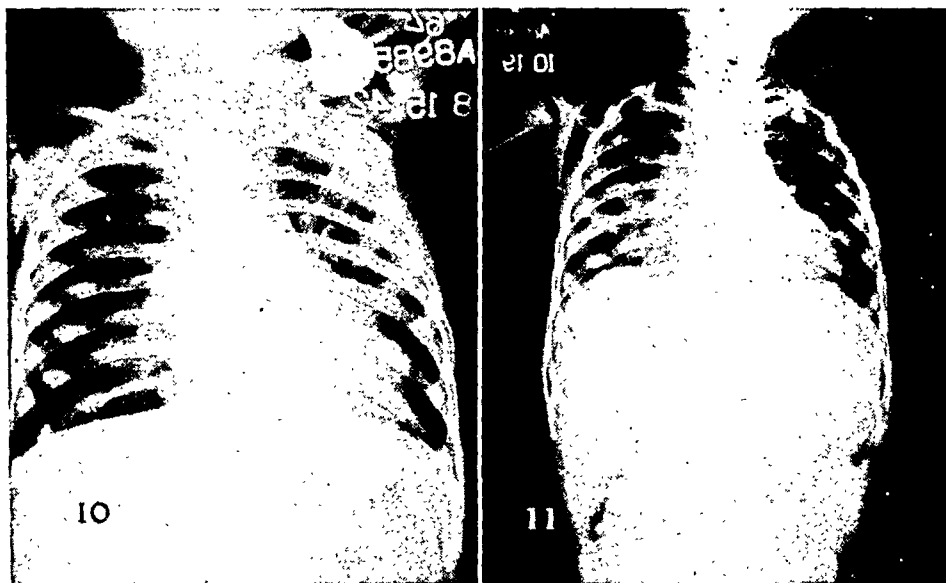


Fig. 10 (Case 4) Chest plate taken August 15, 1942, showing increased hilar markings but no definite infiltration. White blood count 66,000; eosinophils 59 per cent.

Fig. 11. (Case 4) Chest plate taken October 19, 1942, showing marked thickening around the right hilum with some parenchymal infiltration of the soft variety suggestive of tuberculosis. White blood count 64,000; eosinophils 64 per cent.

upper respiratory infection. He was given a purgative and very soon thereafter he had considerable difficulty in breathing and audible wheezing. On the fourth day he had a severe attack of bronchospasm. The family physician diagnosed pneumonia, and the child was hospitalized for four days. He improved during the next two weeks but three days before admission the respiratory difficulty returned, accompanied by a harsh dry cough.

*Physical examination.*—Well developed and nourished. Tonsils moderately enlarged and reddened; anterior cervical lymph nodes palpable. Numerous musical rales throughout both lung fields; no moist rales. The remainder of the examination non-contributory.

*Clinical findings.*—Hemoglobin 9 gms. (58 per cent), white blood count 66,000 with 59 per cent eosinophils (Table IV). A chest plate showed increased hilar markings without infiltration (Fig. 10). The child was sent home and got along very well. He returned ten days later for reexamination. At this time roentgenogram of the chest was essentially as previously noted. Examination of the chest showed nothing abnormal. However, the white blood count was 56,560 with 71 per cent eosinophils. (Blood smears obtained from three siblings and patient's father were studied: one brother had an eosinophilia of 5 per cent without leukocytosis.) The question of eosinophilic leukemia was raised and bone marrow studies were done (Table IV). At this time skin tests to the common-allergens were negative. Weltmann reaction was C. B. 2. Sputum and gastric washings failed to show tubercle bacilli. Schick and tuberculin tests were negative. Stool examinations were non-contributory. The patient was given 120 c.c. of citrated blood without reaction. He was discharged five days after admission apparently feeling well.

He returned two months later for a recheck. In the interim he had had three fairly severe attacks of asthma and a persistent nocturnal cough. According to his mother, he had passed two round worms two weeks previously. On examination

he had a papulo-pustular skin rash over the chest and buttocks. There were occasional coarse inspiratory bronchi at the right base after coughing. Spleen was palpable 3 cm. below the costal margin. Complete blood and bone marrow studies were done (Table IV). Roentgenogram of the chest showed marked thickening

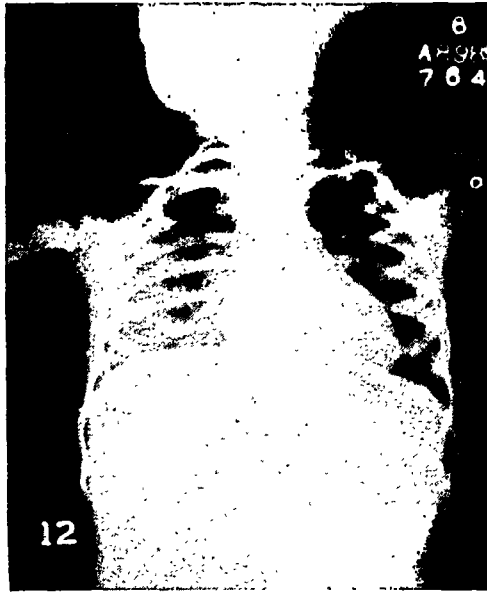


Fig. 12. (Case 4) Chest plate taken July 6, 1943, showing decrease in the amount of peribronchial infiltration on the right. White blood count 10,450; eosinophils 14 per cent.

around the right hilum with a soft parenchymal infiltration. "The appearance is suggestive of tuberculosis" (Fig. 11). He gave a 2 plus reaction to the intradermal injection of 0.1 c.c. of a 1:100 dilution of ascaris antigen. Six months later the child returned for reëxamination. In the meantime he had been dewormed, and repeated stool examinations were negative for ova and parasites. He had been quite well, except for occasional nocturnal coughing. On examination a few moist inspiratory rales were heard at the left base. The spleen was still palpable. Blood and bone marrow studies were repeated (Table IV). Another roentgenogram of the chest showed a decrease in the amount of peribronchial infiltration on the right side and no evidence of recent localized infiltration (Fig. 12). Weltmann reaction was C. B. 5. He returned three months later feeling quite well. The physical examination was entirely non-contributory. The spleen was no longer palpable. White blood count was 10,450 and the eosinophils 14 per cent.

*Case 5.*—A twenty-nine-year-old white woman with a history of asthma of about one years' duration following an acute upper respiratory infection. Roentgenograms of the chest showed a mottled consolidation throughout both lung fields. Moderate leukocytosis and eosinophilia, palpable spleen; afebrile course.

M. D. No. A 56322. This young white single woman was first seen in this hospital February 17, 1941, complaining of frontal and generalized headaches of two months' duration. Nothing was found to account for these headaches. Roentgenograms of the skull and sinuses gave negative findings. There was no family history of allergy. The patient returned two years later in status asthmaticus. Three months previously she had what she called "pneumonia" which was followed within a few

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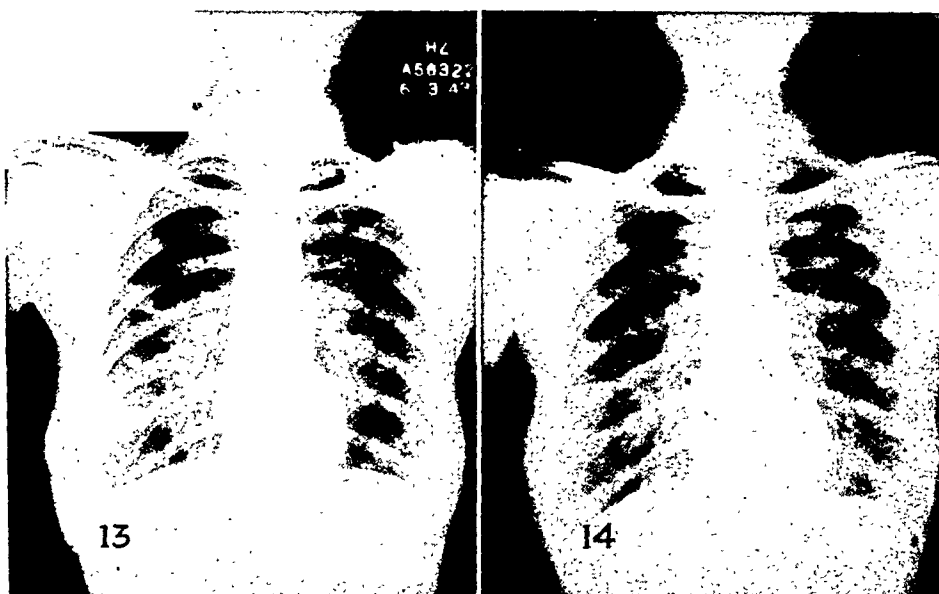


Fig. 13. (Case 5) Chest plate taken June 3, 1943, showing patchy consolidation throughout the mid portions of both lung fields. White blood count 10,050; eosinophils 18 per cent.

Fig. 14. (Case 5) Chest plate taken July 12, 1943, showing some clearing on the right but still considerable consolidation. White blood count 15,350; eosinophils 47 per cent.

TABLE V

DATE	W.B.C.	PER CENT EOSINOPHILS	REMARKS
2/17/41			P.H. Exertional dyspnea—2 years. Bitemporal headaches—3 months. Blurred discs.
5/31/43	27,000	1	Pneumonia 3 months previously. Recurrent asthma. Staticus asthmaticus. Bronchopneumonia by x-ray. Sulfadiazine started.
6/2/43	10,050	18	(Fig. 13).
6/10/43	20,400	23	
6/12/43	17,600 63,000 (B.M.)	25 27 (5% Myelo. E.)	X-ray therapy to lungs.
6/14/43	20,000	25	
6/17/43	16,350	19	
6/21/43	14,200	60	Asthmatic.
6/22/43	19,550	52	
6/28/43	20,000	46	
7/2/43	25,500	40	
7/5/43	13,900	46	Asthma continues.
7/8/43	22,200	43	
7/12/43	15,350	47	(Fig. 14).
7/16/43	16,600	43	Discharged. Still some asthma.

weeks by recurrent attacks of bronchospasm of gradually increasing frequency and severity.

*Physical examination.*—The patient was acutely ill, in severe respiratory distress, moderately cyanotic, with slight papilledema. Tonsils were large and injected.

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TABLE VI

DATE	W.B.C.	PER CENT EOSINOPHILS	REMARKS
2/1/43	20,600	0	Hospitalized. Acute tracheobronchitis. Asthmatic wheezes throughout chest; Chest plate negative. (Fig. 15). Fever subsided 2 days after sulfadiazine was started.
11/12/43	10,250	8	Cough and some wheezing irregularly for the past 10 months. Contracted an U.R.I. one previously and asthmatic since.
12/7/43	8,900	30	Readmitted. Recurrence of tracheobronchitis. Coughing and wheezing. Afebrile. Scattered inspiratory musical and coarse rales throughout chest. No moist rales. Chest plate showed clouding in right upper lobe suspicious of tbc. (Fig. 16).
12/10/43	10,600	34	On sulfamerazine. Improved.
12/11/43	11,400 47,880 (B.M.)	35 9 (4% Myelo. E.)	Afebrile—less asthma.
12/13/43	14,150	29	
12/14/43	8,100	50	Chest clear by x-ray. (Fig. 17).
12/16/43	8,950	29	Discharged
1/10/44	7,800	15	Asymptomatic. Lungs clear by x-ray and on physical examination.

There was moderate emphysema; marked tachypnoea (48 per minute). The chest was full of musical rales with diminished breath sounds at the right base. The spleen was palpable.

*Clinical findings.*—White blood count was 27,000; eosinophils 1 per cent (See Table V). The clinical impression was asthma and early broncho-pneumonia. Roentgenogram of the chest showed a patchy consolidation throughout the mid portions of both lungs (Fig. 13). Kahn and Kline tests were negative. No acid-fast organisms or fusospirochetes were found in the sputum. Culture of the sputum gave *N. catarrhalis*, *N. siccus*, and anaërobic bacteria. Skin tests were inconclusive with slight positive reactions to the intradermal injections of giant and short ragweed, dust and few molds. Immunological studies for *Brucella* were negative. Electrocardiogram was normal. Weltmann reaction ranged between C. B. 4 and C. B. 6. The patient had severe asthma for more than six weeks which did not respond to the usual remedies including oxygen and helium. The patient was afebrile throughout. Soon after admission she developed an eosinophilia and this, as well as the leukocytosis, persisted throughout her hospital stay. She was also given pertussis vaccine as well as a series of x-ray treatments to the lungs without benefit. Repeated roentgenograms of the chest were made and all showed mottled consolidation throughout both lung fields. The last chest plate on July 12, 1943, still showed considerable consolidation but some clearing of the process (Fig. 14). The white blood count was still elevated, but the patient was symptomatically improved.

*Case 6.*—A thirty-year-old married white woman complained of asthma of one month's duration; family and past personal histories negative for allergic disorders. Severe attack initiated by upper respiratory infection. Leukocytosis and moderate eosinophilia. Intractable asthma. X-ray picture of consolidation of right upper lobe with cavitation; afebrile course.

S. K. No. A99019. This patient was admitted on January 30, 1943, complaining of asthma of one month's duration. One month previously she had contracted an

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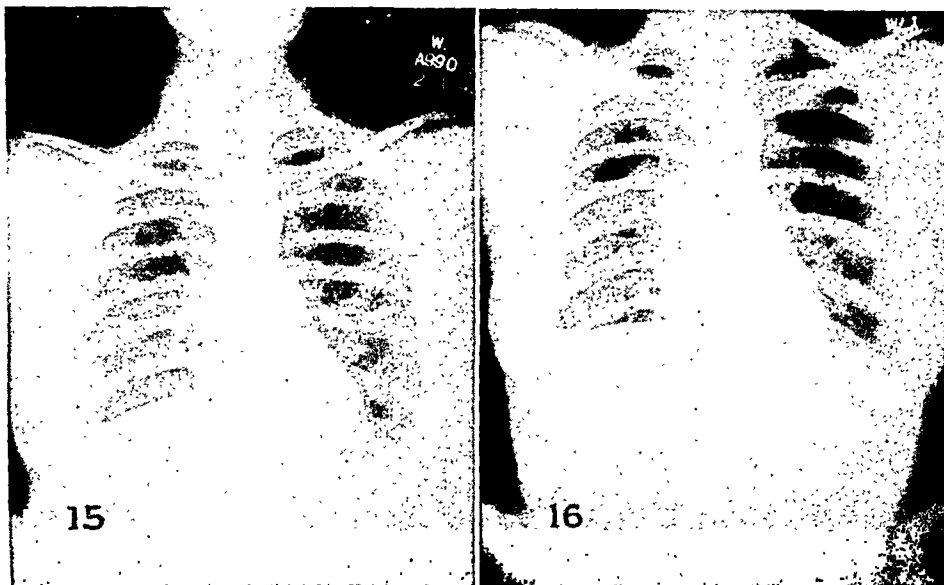


Fig. 15. (Case 6) Chest plate taken February 1, 1943, showing lungs to be essentially clear. White blood count 20,600; eosinophils 0.

Fig. 16. (Case 6) Chest plate taken December 7, 1943, showing a diffuse infiltration in the right upper lobe with a suspicious cavity near the right hilum. The appearance is suggestive of tuberculosis. White blood count 8,900; eosinophils 30 per cent.

upper respiratory infection and the cough and malaise persisted until admission. She expectorated moderate amounts of a mucopurulent material. Four days before admission she had her first attack of bronchospasm; the respiratory distress increased and only temporary relief was afforded by subcutaneous adrenalin.

*Physical examination.*—The patient was well developed, moderately obese, asthmatic, coughing frequently and perspiring freely. The nasal mucosa was hyperemic with a moderate mucopurulent discharge. The paranasal sinuses were clear on transillumination. Pharynx was dry and hyperemic. Limited equilateral expansion of the chest. Tachypnoea (32 per minute). Scattered inspiratory, expiratory musical râles throughout both lung fields. No moist râles heard. Heart rate 112 per minute. No other abnormalities noted.

*Clinical findings.*—Hemoglobin was 15 gms. (97 per cent), red blood count 5,000,000, white blood count 20,600 (Table VI). Kahn and Kline tests were negative. There was a trace of albumin in the urine. Roentgenogram of the chest showed no abnormalities. (Figure 15). Sputum culture yielded alpha hemolytic streptococci, staphylococcus albus, *N. siccus*, hemolytic diphtheroids and anaerobic bacteria. Stool examination was negative.

The patient was afebrile on admission, but on the second hospital day the temperature went to 38.6° C. She was now given sulfadiazine, 1 gm. four times daily and this was continued for five days. The temperature fell to normal on the third day and ranged around 37° thereafter. Her asthma responded to oral ephedrine sulphate with phenobarbital and aminophyllin, and aminophyllin suppositories. She was discharged on the eighth hospital day markedly improved. She returned six months later because of a recurrence of asthma. In the interim she had had an occasional cough and substernal tightness. Following a cold spell of weather the cough became productive of mucopurulent material. She felt that she had contracted an upper respiratory infection, and at this time began to wheeze. Examination in the clinic showed that she was in moderate respiratory distress. Tempera-

ture was normal, pulse 100, respirations 20, blood pressure 120/88. Skin was flushed and moist. Nasal mucosa and pharynx were hyperemic. Numerous musical râles, inspiratory and expiratory, were heard throughout both lung fields. A few

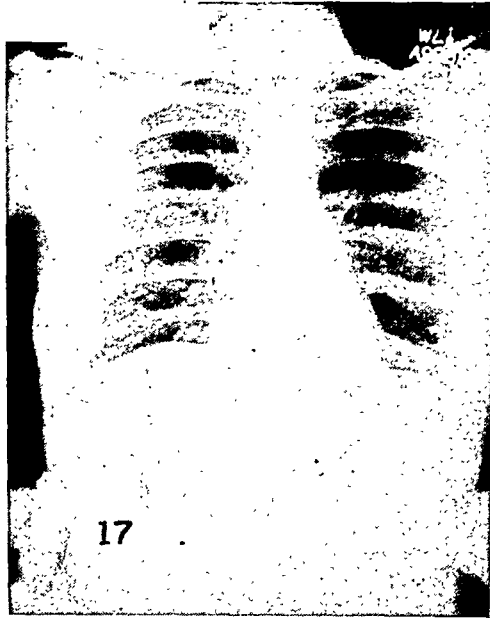


Fig. 17. (Case 6) Chest plate taken December 14, 1942. Previous infiltration to have White blood count 8,100; cent.

moist inspiratory râles were heard after coughing at the lung bases. Complete blood studies were done (Table VI). The patient was instructed to remain in bed, force fluids and to use the remedies previously prescribed. Skin tests done at this time showed slight positive reactions to the intradermal injections of giant and short ragweed, Jersey pine, pussy willow, pecan, chrysanthemum, daisy fleabane, dust, goat epidermis, rice, coffee, alternaria, and oidomycin. Cultures from her sputum yielded alpha hemolytic streptococci, staphylococcus aureus, *N. catarrhalis*, *N. siccus*, and a mixture of anaërobic bacteria. An autogenous vaccine was prepared from these organisms which was combined with the allergens mentioned and desensitizing treatments were started. She got along very nicely until the latter part of November when she developed an acute attack of asthma which did not respond to the remedies which had previously proved effective. She was readmitted to the hospital December 5, 1942, in a status asthmaticus.

*Physical examination.*—The patient was acutely uncomfortable, coughing and expectorating considerable amounts of thick yellow material. The chest was filled with inspiratory, musical and coarse râles; no moist râles were heard and there were no expiratory noises. Temperature was normal.

*Clinical findings.*—Hemoglobin was 16.1 gms. (90 per cent), red blood count 5,150,000, white blood count 8,900 (Table VI). Weltmann reaction was C.B. 2-½. Urine was normal. Brucella agglutinations gave negative findings. Roentgenograms of the sinuses revealed no abnormalities. Stereoscopic views of the chest showed a diffuse infiltration in the right upper lobe with a "suspicious" cavity near the right hilum. The appearance was suggestive of tuberculosis (Fig. 16). The electrocardiogram was normal except for tachycardia and inverted T1. The patient remained afebrile throughout her hospital stay of twelve days. On the second

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hospital day she was given sulfamerazine, 0.5 gm. every four hours, and this was continued for one week. The usual remedies were employed to insure symptomatic relief of her asthma. She was relatively free of asthma during the last three days of her hospital stay. A chest plate repeated on December 14, 1943, showed that the infiltration in the right upper lobe had largely disappeared (Fig. 17). She returned for observation on January 10, 1944, stating that she had felt perfectly well since discharge from the hospital. White blood count was 7,800 with eosinophils 15 per cent. Roentgenogram of the chest showed the lungs to be clear.

### DISCUSSION

The syndrome of allergic pulmonary consolidation is featured therefore by: (1) varying degrees of pulmonary consolidation, at times multiple, often migratory, and recognized by roentgenographic examination of the chest; (2) its occurrence in allergic individuals; (3) a varying leukocytosis and eosinophilia; (4) an afebrile clinical course; (5) persistent, severe asthma; (6) lack of response to the known sulfon drugs; (7) history of frequent upper respiratory infections.

*Pathogenesis.*—We have detailed the histories of six patients, who presented evidences of a pulmonary infiltrative reaction, with slight or no fever, accompanied by a marked eosinophilic leukocytosis of bone marrow origin. The sputum contained many eosinophils. Since no postmortem studies have been made of lungs showing the above type of reaction, its exact nature is unknown, but it is well established that mesenchymal and endothelial tissues can become sensitized, and react in an allergic manner, on subsequent contact with an offending allergen. Why certain individuals show an eosinophilic, pneumonia-like reaction, while others do not, is not readily explicable, but since this type of tissue reaction is encountered mostly in allergic individuals it would seem that the constitutionally hypersensitive person has some tissue peculiarity which results in this type of response.

Although some allergists still doubt the existence of an allergic response to bacteria, the immunological studies of Finland,<sup>7</sup> his co-workers and others, as well as clinical experience, have provided evidence that the tissues can become sensitized to bacterial products, whether they be protein or carbohydrate in nature. Several years ago, one of us<sup>1</sup> reported a number of clinical examples which showed that the skin will develop, in some individuals, an allergic response to various bacteria if sensitized by *B. erysipelatis*. It was demonstrated that subsequent erysipeloid reactions could be provoked by a number of bacteria which had no close immunological relationship to the sensitizing beta hemolytic streptococcus of erysipelas. There is no reason why a similar condition should not obtain in the bronchial tree, i.e., a susceptible individual becomes sensitized to one or a group of bacteria, or their products, in the course of repeated upper respiratory tract infections, and then shows an allergic response of the pneumonic type of reaction to a re-infection with the sensitizing, or some other type of bacterial antigen. All six of our patients gave a history of frequent upper respiratory tract infections.



Harkavy,<sup>8</sup> in a series of recently published studies, has reëmphasized the importance of the vascular system in allergic reactions and has described the various vascular alterations which may accompany the allergic phenomena. Undoubtedly, many of the clinical manifestations of hypersensitiveness are colored by symptoms of vascular origin, and it is generally accepted that the fundamental allergic response is due to disturbances in the vascular system. These disturbances may range from a simple transitory exudation and edema, with or without a perivascular cellular response, to irreversible vascular changes which result in the death of tissues. In many instances, such an injury to the vascular system is accompanied by a striking eosinophilia. This has been demonstrated by the studies of Rich<sup>10</sup> which he describes in his article on periarteritis nodosa. Describing a series of animal experiments, he states "these experiments demonstrate that periarteritis nodosa is one manifestation of the anaphylactic type of hypersensitivity." Careful study of patients with periarteritis nodosa will demonstrate the parallelism between this syndrome and the more severe forms of recognized allergic disturbances."

*Eosinophilia.*—The cause of the eosinophilia remains unknown. Whether it is a response to increased mobilization of histamine, as has been suggested, or to increased need for this substance, supposedly carried by eosinophils, has not been shown. All we can say definitely is that eosinophilia is of bone marrow origin and is part of the general allergic response (Figs. 18 and 19). The degree of eosinophilia does not indicate the severity of the allergic reaction, but marked eosinophilia often accompanies the clinically more severe allergic manifestation.

Chillingworth<sup>5</sup> and co-workers reported experiments on dogs in which they produced temporary emphysema by insertion of an intratracheal ball-valve. All their animals developed leukocytosis promptly and, in many instances, marked eosinophilia. They concluded that the eosinophilia is "reflex" and is caused by expiratory delay with overdilatation of the alveoli. Adrenalin did not modify these eosinophilias. In the same paper, however, they described the effect of adrenalin on two asthmatic patients with eosinophilia and one patient with chronic eczema and eosinophilia. The degree of eosinophilia was reduced materially twenty-four hours after the administration of adrenalin in the asthmatic patients but not in the patient with eczema. The leukocyte count and the eosinophil count were followed carefully over the twenty-four-hour period; no changes in the degree of eosinophilia were observed within one hour after adrenalin administration. This is at variance with the previously reported observations of Camp<sup>3</sup> who maintained that the eosinophils are markedly increased within one hour by adrenalin dosage. We have tried the effect of adrenalin on three of our patients with allergic consolidation and have observed the absence of response as described by Chillingworth. However, we disagree that the eosinophilia of the asthmatic is purely a reflex phenomenon but believe that it is an expression of the allergic state. Certainly, it is

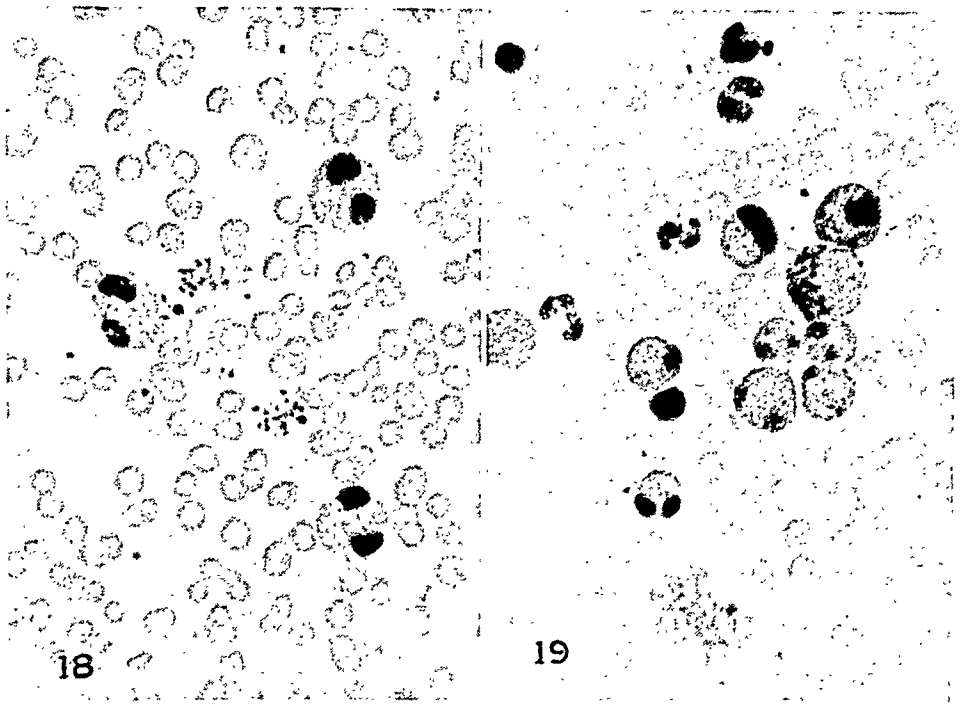


Fig. 18. (Case 3) Eosinophils in peripheral blood.

Fig. 19. (Case 3) Eosinophils in bone marrow.

well known that the eosinophilia of asthmatic individuals persists after the cessation of bronchospasm and in the absence of evidence of alveolar overdistention. The sweeping conclusions of Chillingworth furthermore disregard the marked eosinophilia which often is found in nonasthmatic allergic individuals suffering from atopic rhinitis, eczema and other expressions of allergy. Thomas and Taylor,<sup>13</sup> in a recent article on allergic bronchitis, noted a moderate degree of eosinophilia in over half of their patients; they concluded that a persistent eosinophilia was usually the rule in those who responded poorly to treatment and that it could, therefore, be considered a sign of poor prognosis.

As far as we could determine, the incidence of allergic consolidation of the lung was not an indication of an exceedingly hypersensitive individual, although we realize that methods of evaluating the degree of hypersensitivity in the human are still very inadequate. The degree of skin reactivity to test allergens was certainly not greater in our group of patients with allergic pneumonic reactions than in a comparable group of other allergic subjects; if anything, it was less. It is quite possible that the degree of eosinophilia marks the severity of vascular injury. This is suggested by the occurrence of eosinophilia in such conditions as periarteritis nodosa and Hodgkin's disease. In any event, the eosinophilia is of myeloid origin, a generalized systemic phenomenon and not, as has been previously thought, confined to or initiated by the pulmonary tissue.

Moreover, as illustrated by our sixth patient, a persistent eosinophilia is compatible with complete symptomatic recovery.

*Diagnosis.*—The diagnosis of allergic pulmonary infiltration should offer no difficulty if the patient is carefully studied. The roentgenological findings are varied and by themselves, may prove confusing. In our group of patients the pulmonary involvement suggested either bronchiectasis or bronchopneumonia, or tuberculosis or sarcoid. The differentiation of allergic pneumonic infiltration from *bacterial pneumonitis* (bronchopneumonia, bronchiectasis with pneumonitis) is based on the absence of fever, or severe intoxication and the character of the sputum. The usual polymorphonuclear cell response, without any appreciable eosinophilia, will feature the bacterial type of pneumonitis, which so frequently responds to the sulfon drugs.

In *virus pneumonia* there is, as a rule, a paucity of physical signs with variable x-ray evidence of pulmonary consolidation, but the leukocyte count is normal or decreased and again eosinophilia is lacking. *Ascariasis* may conceivably simulate the circumstances which obtain in an allergic pneumonia. One of our patients (Case 4) was found to be infected with ascaris; however, the disease picture persisted after he was dewormed. Naturally, the stools should be carefully searched for ova and parasites in every instance of eosinophilia.

The x-ray picture of pulmonary and mediastinal *sarcoid* is notoriously variable; since the process is often quite indolent, it may suggest an allergic pneumonitis if it occurs in an asthmatic patient. In two of our patients (Cases 2 and 3) the sarcoid was suggested by the x-ray picture. The correct diagnosis of sarcoid is based upon the x-ray finding of other abnormalities such as cystic areas in the terminal phalanges, hyperproteinemia and the frequently demonstrable skin lesions and lymph node involvement. Eosinophilia of any marked degree is infrequent in sarcoid.

The x-ray picture of the chest in allergic pneumonic infiltration often suggests *pulmonary tuberculosis*, particularly if the process is confined to one or the other of the upper lobes of the lung. In two of our patients (Cases 1 and 6) pulmonary tuberculosis was the initial roentgenological diagnosis. The examination of the sputum which shows numerous eosinophils in the sputum of a patient with allergic pneumonic response, the presence or absence of tubercle bacilli, elastic fibers, Curschmann's spirals and the history, the clinical course and the peripheral leukocytes response should lead to the correct diagnosis.

*Treatment.*—Severe asthma, often of long duration, was in all our patients the outstanding presenting symptom. The same is true of the majority of the cases of a similar type of pneumonic reaction reported in the literature. Our group of patients proved relatively refractory to the usual forms of treatment, including the prolonged use of oxygen, helium and mixtures of these two gases. Several patients were treated empirically by

the administration of pertussis vaccine without benefit. Refractory asthma in a patient with a marked eosinophilia should always suggest the possibility of an allergic pneumonic infiltration and, if cloudy areas can be demonstrated by x-rays, usually it means that the patient's asthma will respond more slowly to the common remedies than does uncomplicated status asthmaticus. Heroic measures are not indicated in such patients and often prove quite disappointing. Because of the prolonged asthmatic seizures, patients with an allergic infiltration of the lungs, particularly in private practice, are given morphine or some similar alkaloid. This is definitely contraindicated, since these drugs produce a contraction of smooth muscle and accentuate the bronchospasm.

Sulfa drugs are useful if there are evidences of a bacterial infection, such as a purulent bronchitis, naso-pharyngitis, or sinusitis, but have no effect on the allergic pneumonic process. We wish to warn against the indiscriminate use of the sulfon drugs in allergic patients, particularly those with an allergic pneumonic infiltration. Aminophyllin by mouth, in combination with ephedrine sulphate and phenobarbital (100 mgm., 15 mgm., respectively), every four hours, and rectal installations of aminophyllin (500 mgm. in 60 c.c. of water), or suppositories of aminophyllin (250 mgm.) have proven quite helpful in relieving the asthmatic distress in most of our patients. The therapeutic response was much slower in this group than in the usual asthmatic. We have rarely used adrenalin since the above-named medications always produced sufficient relief to insure some rest to the patient. Intravenous aminophyllin was resorted to only in very ill patients when there were no detectable evidences of myocardial embarrassment. All the patients were given salt water enemas daily as long as they were severely asthmatic. Fluids were forced and fruit juices were given in large amounts. In addition, every patient received a mild sedative by mouth or rectally once or twice a day, to allay anxiety and induce restful sleep.

#### SUMMARY

The syndrome first described by Loeffler consists of migratory pulmonary reactions occurring as a rule in allergic individuals, accompanied by leukocytosis and a varying degree of eosinophilia. In view of the fact that the exact nature of the pulmonary reaction remains obscure, and since we cannot state whether it consists of an infiltration or an inflammatory reaction, we believe that the term allergic pulmonary consolidation is acceptable, because it does not indicate a specific histopathological change.

The pulmonary changes are usually discovered by x-ray examination of the chest; the usual physical signs of intra-pulmonary change are masked by the auscultatory signs of bronchospasm. A concomitant severe and often intractable asthma is the rule.

The eosinophilia in our six patients is obviously of myeloid origin and persists in a moderate degree after the disappearance of asthma and of the x-ray evidences of pulmonary consolidation.

Our six patients who developed allergic pulmonary consolidation gave a history of repeated upper respiratory infections and the acute episode appears to have been precipitated by a fresh infection in the respiratory tract. Sulfon drugs were efficacious in controlling the acute infection; they are indicated in patients who have purulent sputum. Once the acute infection responds to the sulfon drugs, the clinical course becomes afebrile regardless of the extent and persistence of pulmonary consolidations, leukocytosis or eosinophilia.

Individuals who develop allergic pulmonary consolidation are always severely asthmatic. The asthma tends to persist until the pulmonary consolidation clears considerably or disappears; allergic pulmonary consolidation should be suspected in all individuals with intractable asthma and marked eosinophilia and leukocytosis. Furthermore, it will undoubtedly prove worth while to examine the peripheral blood of patients with intractable asthma; if leukocytosis and eosinophilia are found, roentgenograms of the chest should be taken to demonstrate or rule out the presence of pulmonary consolidation as the cause of the therapeutic failure.

The pulmonary x-ray shadows seen in allergic consolidation are quite variable, and may be mistaken for pulmonary sarcoid, virus pneumonia, tuberculosis and pyogenic pneumonitis.

We believe that allergic pulmonary consolidation is an expression of sensitization to nonspecific bacteria and that it can occur in constitutionally allergic individuals as well as in individuals who acquire the allergic response.

Allergic pulmonary consolidation is often a very severe syndrome which may last for weeks, but so far fatalities have not been observed.

The treatment of allergic consolidation of the lungs is the treatment of the presenting symptom of asthma. Sulfon drugs have no effect on the duration or extent of pulmonary consolidations nor on the degree of leukocytosis or eosinophilia.

#### SUMARIO

El síndrome primeramente descrito por Loeffler, consiste de reacciones pulmonares fugaces que por regla general ocurren en individuos alérgicos, acompañadas por leucocitosis y un grado variable de eosinofilia. En vista del hecho de que la exacta naturaleza de la reacción pulmonar permanece oscura y desde que no podemos establecer si consiste en una infiltración o en una reacción inflamatoria, creemos que el término Consolidación Alérgica Pulmonar es aceptable porque ello no indica un cambio histopatológico específico.

Los cambios pulmonares son generalmente descubiertos por medio de radiografías. Los datos auscultatorios y de exploración habituales se encuentran enmascarados por los signos auscultatorios del broncospasmo. Generalmente se encuentra acompañado de asma intenso y a menudo de mal asmático.

La eosinofilia en nuestros seis pacientes es evidentemente de origen

mieloide y persiste en un grado moderado despues de la desaparición del asma y de los hallazgos radiográficos.

Nuestros seis pacientes que desarrollaron consolidación alérgica pulmonar presentaron una historia de repetidas infecciones del árbol respiratorio superior y el episodio agudo parece haber sido precipitado por una nueva infección del tracto respiratorio. Las Sulfa drogas fueron eficaces para controlar la infección aguda; son indicadas en pacientes que tienen esputo purulento. Una vez que la infección aguda responde a las Sulfa drogas, el curso clínico se vuelve sin fiebre sin importar del grado y persistencia de la consolidación pulmonar, leucocitosis o eosinofilia.

Los individuos que desarrollan consolidación alérgica pulmonar son siempre severamente asmáticos. El asma tiende a persistir hasta que la consolidación pulmonar alérgica se disipa considerablemente o desaparece; consolidación pulmonar debe sospecharse en todos los individuos en status asmáticus y marcada eosinofilia y leucocitosis. Además debe hacerse un hemograma de los pacientes con asma rebelde; si se encuentran leucocitosis y eosinofilia se debe sacar radiografía del pecho para demostrar o excluir la presencia de consolidación pulmonar como la causa del fracaso terapéutico.

Las sombras radiográficas pulmonares son completamente variables y pueden ser confundidas con una neoplasia, neumonía a virus, tuberculosis y neumonitis piógena.

Creemos que consolidación alérgica pulmonar es una expresión de sensibilización no-específica bacteriana y que ello puede ocurrir tanto en individuos de constitución alérgica como en individuos que se hacen alérgicos.

Este es un síndrome intenso que puede durar varias semanas, pero hasta ahora no han sido observados casos de muerte.

El tratamiento de consolidación alérgica de los pulmones es el mismo usado para el asma. Las Sulfa drogas no tienen efecto sobre la duración o extensión de la consolidación pulmonar ni sobre el grado de leucocitosis o eosinofilia.

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### PROSTIGMIN TREATMENT OF PERIODIC HEADACHES

L. Perner and M. E. Aibel (*J. Lab. & Clin. Med.*, 1942, 27:1546) have added to Horton's group of vascular headaches, those headaches skin sensitive to acetylcholine as well as to histamine. They report a new method of treatment based on this theory. The authors studied a series of sixty patients with periodic headaches, migraine and histamine cephalalgias. All patients in this group were skin sensitive to histamine and/or acetylcholine.

Based on the action of prostigmin in liberating and preserving acetylcholine, the authors thought that repeated acetylcholine "shocks" produced by small increasing doses of prostigmin might produce a desensitization of the patient to acetylcholine in the same manner as histamine cephalalgias are desensitized to histamine by Horton's technique. The procedure is as follows: A solution consisting of one 15-mg. tablet of prostigmin bromide, dissolved in one ounce of water, is administered in doses of one drop three times a day, progressively increasing each dose by one drop until 30 drops are reached. Then 30 drops were given each day for one week, and thereafter every other day until the patient was free from symptoms for a reasonable length of time.

The skin reaction in 40 per cent of the patients tested decreased with desensitization treatment with prostigmin. The acetylcholine wheal and flare were always reduced in size after treatment. All of the periodic headaches, whether of the histamine type described by Horton, or migrainous, were relieved definitely to a great extent.

Perner (*Dis. Nervous System*, 1943, 4:177) further reports the results obtained in treating forty-six patients with periodic occipital headache by this method of treatment. Hypersensitivity to acetylcholine or histamine on skin testing was demonstrated in all. In all except three of the cases, the occipital headaches were considered to be vascular in origin, caused by an accumulation of metabolites causing vasodilatation.

## SKIN REACTIONS TO PATCH TEST WITH HUMAN DANDER

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IN a previous report evidence was presented demonstrating the existence of an allergen in human dander, human hair from the scalp, and seborrhoeic eczema scales.<sup>3</sup> The allergen was not detected in epidermis from the general body surface, hair from the scalp of a newborn infant, or in hair and other contents of a dermoid cyst of the ovary. The presence of the allergen was demonstrated by means of skin reactions. These were obtained in certain patients with atopic eczema when the tests were performed by the *scratch* method. *Intradermal* tests in passively sensitized skin sites were positive, thus demonstrating the presence of reagins. *Patch* tests were not performed on any of these patients. Later, however, it was decided to do tests by this method on some of the same and on other patients.

### EXPERIMENTS

*Materials and Methods.*—Human dander (dandruff) from the scalps of normal adults was obtained by the use of clean fine combs. The dander was mixed with just sufficient petrolatum to make a thick paste, a thin layer of which was spread on a small piece of blotting paper and applied directly to the skin as a patch test. The patches were allowed to remain in position for two days. Readings were made at the time of removal of the patch, fifteen minutes later and in some cases on the following day and one week later.

For scratch tests the dander was rendered oil-free by ether extraction. It was then extracted in 50 per cent glycerine, the volume of glycerine used being approximately five times that of the loosely packed dander. The extract was passed through a Seitz filter and used undiluted for scratch tests directly on patients. For intradermal tests in passively sensitized skin sites 1-100 carbolized buffered saline dilutions of this extract were used. Tests were performed on:

1. Twelve children with eczema. These were routine office admissions, not selected cases.
2. Nine patients with atopic eczema, aged twelve to twenty-six years.
3. Twelve atopic children and adults without atopic eczema.
4. Twenty-five nonatopic children and adults including eight newborn infants.

The criteria for the diagnosis of atopic eczema were the presence of typical clinical lesions, positive skin reactions to foods or inhalants (scratch method), positive family history of atopy and, in some cases, the presence of other manifestations of atopy in the patient.

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# PATCH TEST WITH HUMAN DANDER—SIMON

## TABLE I. SKIN REACTIONS TO HUMAN DANDER

Case No.	Age	Clinical Diagnosis	Patch Test	Scratch Test	Passive Transfer
1	5 mos.	Eczema*	—	—	—
2	12 mos.	Eczema*	++	—	—
3	12 mos.	Eczema*	++	—	—
4	16 mos.	Eczema*	++	—	—
5	17 mos.	Eczema*	+++	—	—
6	20 mos.	Eczema*	+++	—	—
7	20 mos.	Eczema*	—	—	—
8	2 yrs.	Eczema*	—	—	—
9	3 yrs.	Eczema*	+++	—	—
10	5 yrs.	Eczema*	—	—	—
11	5 yrs.	Eczema*	++	—	—
12	5 yrs.	Eczema*	++	—	—
13	11 yrs.	Atopic eczema	—	—	—
14	12 yrs.	Atopic eczema	—	+++	+++
15	17 yrs.	Atopic eczema	—	++	++
16	17 yrs.	Atopic eczema	—	+++	+++
17	19 yrs.	Atopic eczema	—	+++	+++
18	21 yrs.	Atopic eczema	—	+++	++
19	22 yrs.	Atopic eczema	—	++	++
20	22 yrs.	Atopic eczema	—	++	++
21	26 yrs.	Atopic eczema	—	—	—
22	3 mos.	Asthma	—	—	—
23	21 mos.	Asthma	—	—	—
24	3 yrs.	Asthma	—	—	—
25	6 yrs.	Asthma	—	—	—
26	6 yrs.	Asthma	—	—	—
27	8 yrs.	Asthma	—	—	—
28	12 yrs.	Hay fever	—	—	—
29	25 yrs.	Hay fever	—	—	—

*Results.*—A positive reaction to patch test was manifested by an area of redness, slight swelling and numerous fine, superficial elevations at the site of application of the dander. This reaction was seen a few minutes after removal of the patch and also on the following day. Seven days later a slightly scaly eczematous patch was clearly visible. Nine positive reactions were obtained to patch tests (Table I). With one exception these occurred in young children with eczema; of twelve such cases, eight gave positive reactions. The exception was that of a four-year-old child without clinical manifestations of atopy. His mother, however, had childhood eczema and his mother's sister has asthma. It is interesting to note that while the older children and adults with atopic eczema gave negative reactions to patch tests with human dander, in seven of nine cases eleven

# PATCH TEST WITH HUMAN DANDER—SIMON

Case No.	Age	Clinical Diagnosis	Patch Test	Scratch Test	Passive Transfer
30	27 yrs.	Hay fever	-	-	
31	30 yrs.	Hay fever	-	-	
32	40 yrs.	Hay fever	-	-	
33	49 yrs.	Hay fever	-	-	
34	Newborn	Nonatopic	-	-	
35	Newborn	Nonatopic	-	-	
36	Newborn	Nonatopic	-	-	
37	Newborn	Nonatopic	-	-	
38	Newborn	Nonatopic	-	-	
39	Newborn	Nonatopic	-	-	
40	Newborn	Nonatopic	-	-	
41	Newborn	Nonatopic	-	-	
42	2 yrs.	Nonatopic	-	-	
43	2 yrs.	Nonatopic	-	-	
44	2 yrs.	Nonatopic	-	-	
45	3 yrs.	Nonatopic	-	-	
46	3 yrs.	Nonatopic	-	-	
47	4 yrs.	Nonatopic	-	-	
48	4 yrs.	Nonatopic	++	-	-
49	4 yrs.	Nonatopic	-	-	
50	5 yrs.	Nonatopic	-	-	
51	5 yrs.	Nonatopic	-	-	
52	7 yrs.	Nonatopic	-	-	
53	9 yrs.	Nonatopic	-	-	
54	35 yrs.	Nonatopic	-	-	
55	38 yrs.	Nonatopic	-	-	
56	40 yrs.	Nonatopic	-	-	
57	44 yrs.	Nonatopic	-	-	
58	47 yrs.	Nonatopic	-	-	

\*For information regarding type of eczema refer to Table II.

years of age or older there were positive reactions by the scratch method and in all of these reagins were demonstrated by local passive transfer. Reactions to patch and scratch tests on the control subjects, with the one exception noted above, were negative (Table I).

An analysis of cases Nos. 1 to 12 is given in Table II.

## DISCUSSION

The etiologic significance of positive reactions to patch tests with human dander in children with eczema appears to be worthy of investigation. All children undoubtedly have daily contact with human dander, either from their own scalp or from that of parents, nurse or other attendants.

# PATCH TEST WITH HUMAN DANDER—SIMON

TABLE II. ANALYSIS OF THE TWELVE CASES OF INFANTILE AND CHILDHOOD ECZEMA

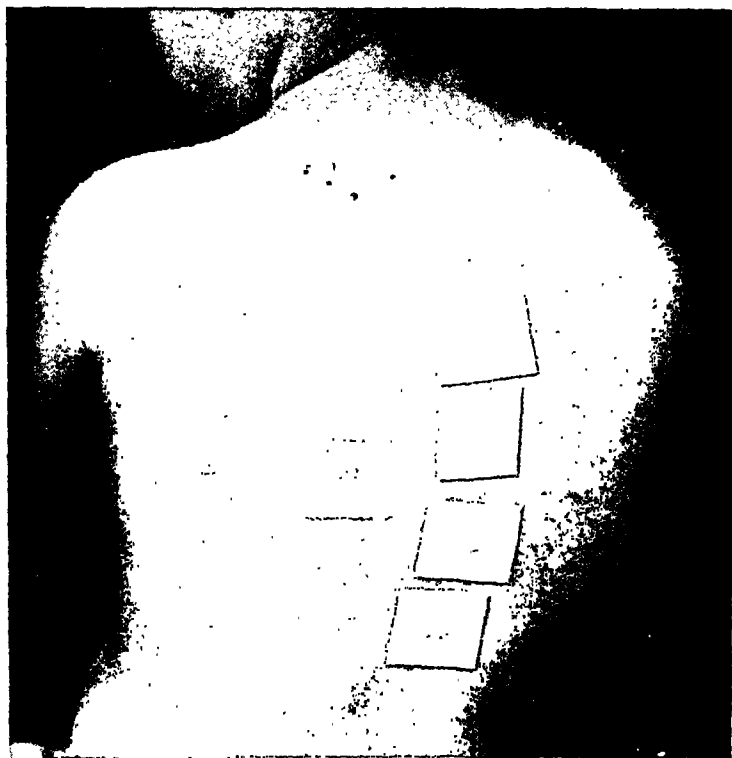
Case No.	Age	Character of lesions	Location of lesions	Scratch tests to foods and inhalants	Family History of atopy	Patch test to human dander	Scratch test to human dander
1	5 mo.	Papular circumscribed Erythematous	Upper and lower extremities, face	Egg + + + +	+	-	-
2	12 mo.	Papular Erythematous Diffuse, scaly	Face Arms Forearms Legs	-	+	++	-
3	12 mo.	Erythematous Diffuse Scaly	Face Forearms Legs Thighs	Egg + + +	+	++	-
4	16 mo.	Papular, scaly Diffuse and circumscribed	Upper and lower extremities. Popliteal spaces. Thumb	-	+	++	-
5	17 mo.	Diffuse, scaly on face. papular and erythematous	Face. Cubital spaces. Legs Thighs	Egg + + + +	+	+++	-
6	20 mo.	Erythematous Diffuse Scaly	Face Wrists Cubital spaces	-	+	+++	-
7	20 mo.	Erythematous circumscribed Patchy areas	Thighs only	-	±	-	-
8	2 yrs.	Erythematous circumscribed and diffuse	Arms. Forearms Popliteal spaces Behind ears	-	+	-	-
9	3 yrs.	Diffuse Scaly	Right cubital space. Right wrist. Right forearm	-	-	+++	-
10	5 yrs.	Erythematous circumscribed	Face. Cubital and popliteal spaces	-	±	-	-
11	5 yrs.	Diffuse Scaly	Face. Arms Forearms Popliteal spaces	-	+	++	-
12	5 yrs.	Erythematous Scaly Diffuse	Face. Forearms Cubital spaces Thighs. Legs	Wheat ++	+	++	-

If human dander should actually prove to be an important causative factor in infantile and childhood eczema, the fact would explain several perplexing problems. For example, it would account for the fact that the disease is not present at birth but often begins several weeks or months later, after a period of time required for exposure and development of hypersensitiveness. In some cases this condition develops while the child is still nursing the breast and before it has received any food other than mother's milk. Allergy to human dander would account for the occurrence of the disease in certain cases in which all skin tests performed with foods and inhalants are negative. It would also explain the frequent failure of food elimination to result in healing of the lesion.

While the hypothesis offers explanations for several hitherto unexplained facts, it also poses several questions. Is this reaction an atopic

## PATCH TEST WITH HUMAN DANDER—SIMON

response of the epidermis or is it a reaction of the superficial layer of the corium, due to "transepidermal penetration"?<sup>1</sup> Is it possible that this contact reaction to human dander represents the so-called "seborrhoeic element"<sup>2</sup> of infantile eczema and that this element is in reality an allergic,



### REACTIONS TO TESTS WITH HUMAN DANDER

*First row (on the left):* Positive reactions to three different specimens of dander from normal adult scalps. Negative reaction to "cradle cap" from an infant, aged three months.

*Second row:* Negative reaction to patient's own eczema scales. Positive reaction to patient's own dander from scalp. Negative reaction to wool.

*Third row:* Four patches in position.

*Fourth row:* Tests done seven days before photograph was taken showing one strong reaction still clearly visible.

probably atopic, response to surface contact with human dander having its source chiefly in the scalps (and secondarily on clothing, et cetera) of parents and others, possibly even the child himself? Do children sometimes "outgrow" their eczema because they get too large and too heavy to be held comfortably by their mothers? Why do the lesions occur on the face, neck, and flexures of the arms and legs much more frequently than on the scalp? Why does the skin, in a significant proportion of cases, improve greatly or clear up entirely in hot weather? Is the allergen present also in the lesions? What is its biologic origin? Is it cornified epidermis? Or does it have its origin in some microorganism? These and other questions can be answered only by further study.

It must be emphasized that no one allergenic excitant will account for

## PATCH TEST WITH HUMAN DANDER—SIMON

all cases of atopic eczema, a disease in which multiple sensitivity is the rule. In fact, some cases (a rather small percentage, however) may be explained on the basis of food allergy. Attention is called to the fact that the type of response to patch test described herein is not unique but appears to be identical with that described by Albert and Walzer,<sup>1</sup> obtained with silk, feathers, et cetera, in atopic children; not exclusively, however, in patients with atopic eczema.

### SUMMARY

A skin reaction to patch test with human dander is described. The reaction was elicited in eight of twelve children with eczema and in one child without eczema. Other children without eczema gave negative reactions. Adults with and without atopic eczema gave negative reactions to patch tests but seven of nine persons, eleven years of age or older, with atopic eczema gave positive reactions to scratch test with human dander. In all of the latter, reagins were demonstrated by passive transfer.

It is suggested that the etiologic significance of these reactions to patch test with human dander is worthy of investigation.

### SUMARIO

Se ha descrito una reacción cutánea a la prueba de "patch" con caspa o epitelio de seres humanos.

La reacción fué descubierta en 8 de los niños con eczema y en un niño sin eczema. Otros niños sin eczema dieron reacciones negativas.

Adultos con o sin eczema atópico dieron reacciones negativas a la prueba de "patch," pero 7 de 9 individuos, de edad de 11 años o más, con eczema atópico, dieron reacciones positivas al método de escarificación con caspa. En todos los últimos casos, la existencia de reaginas fué demostrada por el método indirecto o de transporte pasivo.

Se hace la sugestión que la significación etiológica de estas reacciones a la prueba de "patch" con caspa de seres humanos vale ser investigada.

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## FOOD ALLERGY

### The Role of Food Allergy in Internal Medicine

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FOOD allergy is a problem which concerns every physician in the practice of medicine. While it is not necessary that every doctor be able to make a complete diagnosis of food sensitization, it is important that he be sufficiently informed on the subject that he may correctly evaluate it in the differential diagnosis. He should also be able to advise the patient concerning the nature of the procedures necessary to the evaluation of this problem.

This paper is based upon more than a score thousand deliberate feeding tests and the subsequent follow-ups made during the past twelve years. It is hoped that at least part of the information obtained from this study will be an aid to the physician not specializing in allergy, in the evaluation of food sensitization.

#### DEFINITION

Food allergy, in this communication, refers to those foods which, under correct conditions of testing, produce definite clinical manifestations. These reactions must be not only constant with repeated trial, but also must exhibit specificity. Thus, for example, one is considered allergic to a food if it (a) increases his blood pressure; (b) produces ulnar neuritis; or, (c) induces asthma or hay fever. This restricted definition excludes foods which give skin reactions and foods suspected of causing symptoms, but which, in either instance, cannot be proved by deliberate test.

#### INCIDENCE OF FOOD ALLERGY

Vaughan<sup>1</sup> has indicated that about 60 per cent of the general population is subject to food allergy, of which 50 per cent is considered minor, not a medical problem, and 10 per cent is major, requiring medical attention.

The incidence of food allergy in patients with common allergic syndromes may vary from only one sensitization in the more fortunate allergic, to practically every food used regularly by the patient. Contrary to general opinion, the number of foods to which one becomes sensitive increases with age—adults having more food allergies than children. In hay fever the average is about five foods, in perennial nasal allergy it is nearer seven, while in asthma it is above ten per patient. This is what would be expected since the frequency of use of a given food is a major factor in precipitating an allergy to it. There are several other conditions which

<sup>1</sup>Presented before the Southwest Allergy Forum, Fort Worth, Texas, May, 1941. Presented as a symposium on Food at the Fourth, Fifth and Sixth Annual Forums on Allergy. Read February 22, 1944, at the Doctors' Dinner Club, Oklahoma City, Oklahoma.

influence the development of food allergies. These are infections, particularly measles, whooping cough and especially influenza. These four precipitating causes of sensitization are: frequency of feeding, measles, whooping cough and influenza. They are, however, dependent upon another factor which I have called "the inherent tolerance for foods."

Patients vary greatly in their ability to eat the same food repeatedly before becoming sensitive to it. This tolerance, in turn, predicates the eventual degree of relief that these patients will obtain, other factors being correctly treated. The severity of symptoms in the untreated patient is not a guide to the degree of food tolerance. The percentage of compatible foods among those used almost daily, however, is a reliable indication of this inherent tolerance. It is important to determine early in the treatment of a patient as to whether his tolerance for foods is high or low. If it is true that the patient has become sensitive to 70 per cent of the foods used daily, it is to be expected that he will also become sensitive to many of those substituted for foods eliminated because of sensitivity. This fact formulates the real criticism of the elimination diet, namely—any patient who is so ill that one must use a diet of three or four foods to analyze his food allergies, is too ill to be kept on such a diet. It has been proved on many occasions that a week's constant use of a food will induce an active allergic state and that the use of the restricted diet often increases the patient's total number of allergies.

#### CLINICAL CONDITIONS DUE TO FOOD ALLERGY

Where does one expect to find food allergy? Obviously it is a factor in asthma and perennial nasal allergy and, to a lesser extent, in seasonal hay fever. It is also a common cause of headaches, hives and infantile eczema. These are the common allergic syndromes in which food allergy occurs more or less constantly, but there are a great number of other clinical syndromes in which food sensitizations are of import. These are: arthritis, sciatica, lumbar pain, ulnar neuritis, insomnia, hypertension, toxemia, tachycardia, anginal attacks, nervousness and general irritability as well as bladder irritation, hematuria, albuminuria and vertigo.

The variety of conditions in which foods have been found to be a factor naturally prompts the question as to what criteria one may use as a guide for initiating studies for food allergies. What are the indicators that food sensitization may be the cause of a given set of symptoms? It is not the failure to find any other explanation for the condition, but rather the presence of several definite facts which may be determined partly by history and more fully by observations.

#### CRITERIA INDICATING FOOD SENSITIZATION

If certain symptoms could be due to foods and no organic cause has been found, these criteria will be a useful guide providing at least two of the three points exist in a given case.

1. The patient, from time to time, will have itching of the nose or the

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naso-pharynx. If this is denied upon history taking, have observations made over a period of time. This sign is seldom absent in food allergy.

2. At various times the patient will retire free of symptoms and either be awakened out of sleep with an attack of asthma or nasal allergy or develop such upon arising. Again he may be subject to the constant daily level of symptoms and awaken from sleep with a definite exacerbation or have a flare immediately upon arising.

3. There should be exacerbations of typical symptoms which last two to three days. These may be either superimposed upon constant symptoms, or may develop and continue in a patient otherwise symptom-free.

While there are patients in whom food sensitizations occur in which not one of these three criteria are present, nevertheless, these are reliable guides to warrant dietary studies. These criteria are dependent on the fact that practically every allergic individual is sensitive to foods that are used intermittently and will, therefore, produce exacerbations.

### VALUE OF SKIN TESTING

Every informed physician today knows that skin testing for foods is not entirely reliable, whereas testing for inhalants is of exceptionally high value. One will find in large groups of patients that at least 20 per cent of the foods actually the cause of allergic symptoms will give skin reactions, while a positive test is associated with clinical reaction after ingestion of the food about 40 per cent of time. There is no evidence to indicate that frequent skin testing and retesting with food extracts will do other than to add to the general confusion.

It may be stated without fear of successful contradiction, that one should not stop using skin tests, neither should they be used unless they are supported by immediate and definite diagnostic programs in connection with such tests. Vaughan<sup>2</sup> covered this subject with consummate finality when he stated, "Skin tests represent a point of departure in the therapeutic program."

The basis of all other diagnostic measures is the demonstration of a specific allergic reaction by deliberate ingestion of the food. Since October, 1932, I have completed over a score thousand of individual feeding tests. It is my opinion, based upon this experience, that the most valuable fact in the diagnosis of food allergy is a knowledge of its nature and mechanism of reaction. Further, this information should be visualized so that it may be applied in clinical practice.

### THE NATURE OF FOOD ALLERGY

Food allergy may be classified as being either (1) fixed—(constant sensitization), or (2) cyclic—(intermittent sensitization). The fixed food allergy is one that is not affected by the frequency of the food in the diet. Even if one has not eaten the food for many years, the first ingestion of it is followed by definite, often violent, symptoms.

The cyclic food allergies are those that become clinically evident with



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the use of the food and tend to disappear with omission of the food. In other words, the presence or absence of an allergic status is determined by the incidence of the food in the diet. The course of such an allergy, briefly, is as follows:

If one uses a food every day or so, he may be allergic to it but never suspect it as a cause of symptoms. It is common to feel better after the

### THE CYCLIC CHANGES

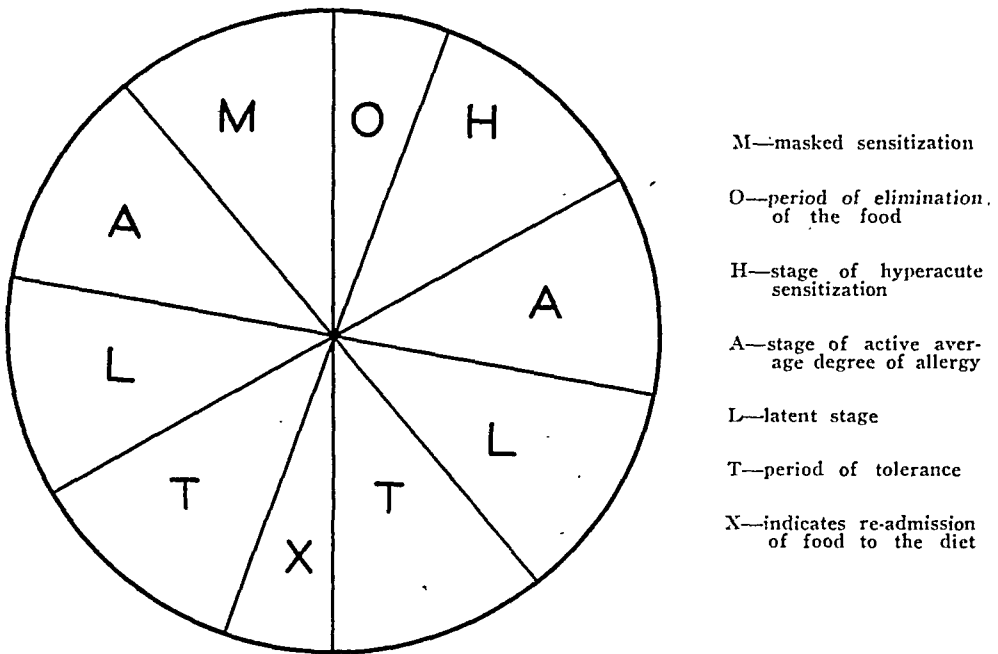


Fig. 1. In this diagrammatic outline of the changes in food allergy, time is conceived as going clockwise. The circle is broken down into three phases, each of which has several important subdivisions.

meal at which this food is used, than before mealtime. This is called a masked food allergy. When the food is eliminated long enough that all symptoms due to its last ingestion have ceased and it is eaten again, it may—and often does—produce increased and sometimes severe symptoms which occur shortly after the meal. If the food is thereafter continuously avoided except for tests, these changes will occur. First, there will be an active but decreased clinical reaction, after which there develops a latent type of sensitization. In this latter state, symptoms are not observed if the food is eaten, for example, on Tuesday, but then do occur following the use of the same food on Friday or Saturday of that same week. With further avoidance, one gains tolerance to the food. If, at that time, it is readmitted to the diet and used with definite regularity, these stages of sensitization will recur—first the latent and then the active state of sen-

sitization. Should the food be used frequently it will become a masked food allergy.

Thus, one has completed a cycle of responses to the same food, these variations being mediated by either the omission or use of the food.

Cyclic food allergy is of three clinical types:

1. *The perennial*.—This is a primary food allergy.
2. *The concomitant*.—This is a food allergy, clinically evident only while one inhales an allergen—for instance, ragweed. It is highly specific.
3. *The thermal*.—These are of two types, the first being a sensitization that is clinically evident, but very mild in warm weather. It becomes of paramount importance when the patient breathes cold air, or otherwise approximates the chilling effect of the inhalation of cold air. The second type of thermal sensitization does not evidence itself until the patient is exposed to cold air or is chilled at, or below, his critical level.

I wish to emphasize that the idea of changes in food sensitization is not new as many allergists have reported and published diagrammatic outlines of such changes. Our visualization of the subject is slightly different and seem to fit in with clinical factors very well.

*Phase I. Changing Response to Foods*.—This stage is the period of time in which the effect of foods change from masked or non-suspected allergens, to reactors associated with immediate and often hyperacute symptoms following ingestion. It consists of several closely related sequences of events.

- (a) In the first period of this phase, called the masked stage, the patient will be repeating the food in the diet before the symptoms, produced by the previous ingestion, have entirely subsided.
- (b) The second feature is the omission of the food until all symptoms produced by the previous ingestion have subsided.
- (c) The final period of this phase is the reintroduction of the food into the diet at the end of period "b" above.

The clinical importance of this phase may be summed up as follows:

1. The first and most important fact is that neither the patient nor the physician can tell, with certainty, if a patient is allergic to a food that is used under conditions which will allow masking of reactions.
2. Except for fixed food allergies, all the hyperacute and severe reactions, all the definite exacerbations of symptoms that affect patients for three to five days at a time, which are due to foods at all, are due to foods in which either by accident or deliberate intention, the successive steps of Phase I have taken place. Reactions from foods having masked reactions, will vary all the way from mild definite symptoms to collapse in ten min-

utes after ingestion, when previously the patient may have felt better after its use.

3. Since these reactions normally last three days in warm weather and may continue five days in winter, one will be on the alert for multiple causes if symptoms do not subside in due course of time.

4. The occurrence of hyperacute reactions or definite flares at once suggests an intermittent cause of such reaction. This fact prompts one to search for this type of reactor.

5. It can be seen that it is important to know not only what a patient eats, but also how he eats. Such information can be obtained only from a dietary record.

6. One can never accept any patient's or physician's statement based upon history and skin tests only, that certain foods either do, or do not, cause allergic reactions.

7. Because of masked allergies, there is often confusion on the part of the patient as to the causative factors. It is the rule that if the patient thinks nearly all foods bother him, he is sensitive to one common food that is obtained in many foods. The best example of this is corn. Conversely, if he reports that no matter what he eats he has about the same amount of trouble, it is very apt to be due to a common food used daily.

8. The complaint of the patient with masked allergies and his actual symptoms are not the same. He states he has trouble as soon as he arises, again around 10:00 to 11:00 A. M., again about 4:30 and around 9:00 to 10:00 P.M., and if the degree of allergy is great enough, in the middle of each night. Actually, in addition he has short, mild flares after each meal.

9. A patient not knowing the facts detailed here, may make changes in how he eats that will result in severe symptoms, although he has not changed the actual foods used. You may deliberately make these same changes for diagnostic purposes.

10. You may expect symptoms ranging all the way from a mild itching of the nose to collapse within ten minutes after ingestion in patients who test foods in the final period of Phase I.

*Phase II. Decreasing Degree of Sensitization.*—The three periods of this phase are—the period of active sensitization, which in turn is followed by that of latent sensitization and, this, in turn, by tolerance for the food. These three periods are not abruptly and sharply defined but fuse into one another to make these changes progressive and less spectacular than the changes which occur in Phase I. The active stage of sensitization is simply less in degree, but all reactions are definite and quite immediate. When the latent state is reached, immediate symptoms are very mild, and one must observe for flares during the night or the next morning, to detect reactors.

Tolerance for a food may be assumed when no demonstrable symptoms can be produced by its ingestion. It is a relative, not absolute tolerance.

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The clinical significance of this phase may be summed up as follows:

1. It may take as little as twelve days to as much as two years to pass through the three periods of Phase II.
2. It is very difficult to determine with finality the effect of foods in the latter part of this phase. Any commitments made to the patient should be made with due regard to these facts.
3. Single feeding tests are not of themselves a sufficient means of diagnosis in the latent sensitizations.
4. When patients have had foods removed from their diets following deliberate feeding tests, they should not have these foods replaced without taking into consideration the changes which have resulted from omission and the changes which will occur in the third phase of the cycle.

*Phase III. Increasing Degree of Sensitization.*—If, when the patient has acquired tolerance for a food, it is replaced in the diet and used as it was before the diagnosis of allergy was made, the sensitization will recur. The latent reactions come first, then active sensitization returns so that after each ingestion symptoms occur. If the frequency of the food in the diet is three or four times weekly, the stage of masked allergy will be produced. These are the important clinical features of this phase:

1. The change from tolerance to active sensitization may occur within one week.
  2. If a food is added when the patient tolerates it, and it is kept in the diet continuously, masked symptoms may be produced without the patient or physician suspecting it as a cause of reaction.
- Symptoms which begin insidiously and gradually increase, are typical of foods added to the diet in this period of the cycle.
3. Foods used at intervals of seventy-two hours may mask their symptoms.
  4. It is not correct to tell a patient, who has been off a food for months or more, to go home and eat a lot of it and see if it produces symptoms.
  5. When patients are seen who have been off foods for a long enough time to have gained a tolerance for the food, do not destroy this tolerance. Evaluate all the factors concerned before issuing instructions for the use of such foods. It is as important to a patient to have his tolerance for a food preserved as it was for him to know originally that a given food was a cause of symptoms.

### CLINICAL APPLICATION OF THE CYCLIC CONCEPT

The value of the cyclic concept is only in that it helps one to visualize the dynamic changing nature of food sensitization. It is important to realize the rapidity of the changes in all three phases, but particularly in that of the decreasing and increasing degrees of sensitization (Phase II and Phase III).

There are several facts of clinical importance that have not been detailed under the headings of the three phases. These will be mentioned briefly.

First, do not assume that because a diet is correct for a patient in the month of May, that it will be satisfactory in September (concomitant allergy to ragweed). Continuing, do not predicate what the diet must be in wintertime, if the diagnosis has been made and the patient freed of all symptoms in the summer months.

Second, patients with primary food allergies must follow their diets any place in the country to remain symptom-free, while those with concomitant reactions may use foods with impunity in certain areas.

Third, the degree of a patient's inherent tolerance to foods can be judged best by the response upon testing the ten most common foods in the diet. If over 50 per cent of these cause trouble, as the percentage increases, the inherent tolerance is lower, while if over 50 per cent are compatible as the percentage agreeable increases, the inherent tolerance is higher. A patient with a low inherent tolerance for foods is a difficult patient to handle. He must not be restricted as much in his diet as the patient with a high inherent tolerance.

There are several other features concerning food reactions that aid one in diagnosis. Severe reactions practically always start soon after ingestion. Patients who react within one hour after ingestion will have the highest percentage of symptoms commencing within five minutes after eating, the next highest at ten minutes and very few begin as late as forty-five minutes. Such reactions, even if the food is used but once, will be clinically evident for about forty-eight to as much as seventy-two hours. Again it is important to know that in over 20,000 deliberate feeding tests, no symptoms have ever been produced by the single use of a food that persisted over five days and, this only, when the patient developed either the lung or sinus secondary reaction with the production of purulent discharges.

The longer the patient has avoided the food, the less immediate and the less definite the symptoms. It becomes increasingly important to know about late reactions, i.e., the middle of the night and the next morning upon arising.

The patient cannot eat so little of a food that it is not to be considered etiologic. The keystone of allergic studies for foods is to have a patient upon a known diet, the patient being symptom-free for at least a week on such a diet. This will require a diet record. No food studies can be exploited to their fullest extent without such records.

Local reactions of the foreign protein type, whether due to vaccines, endocrine products or vitamins, exert a non-specific depression of allergic reactions for varying periods of time. Improvement following their use is not of itself an indication that the effect is specific.

Patients with inhalant allergies may have toxic symptoms from foods at a lower level of sensitization than those required to produce perennial nasal allergy or asthma. The importance of this fact is that many people have toxic symptoms from foods but do not exhibit classical allergic syndromes.

No treatment for a food allergy is adequate if the patient is told only

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that he is allergic to a given food. He must be taught how, when, and where he will contact this food. Special instruction sheets are needed for corn, cottonseed, wheat, egg, milk, soybean, flaxseed and karaya gum, as well as many others.

It is useless to feed patients foods to which they are allergic in an attempt to build them up. More often than not, patients on restricted diets who lose weight, do so because they are still using foods to which they are sensitive. The use of foods to which patients are allergic will add weight by means of allergic edema, but this is not a true gain of weight.

It is to be emphasized again, that one can judge the specificity of food reactions, not by the improvement that follows their elimination, but by the effects produced by the correct testing of the food. Examples of this are common but only one need be mentioned. A patient who gave a large skin reaction to wheat was freed of all symptoms by the avoidance of wheat. He was actually allergic to malt which was not used during the omission of wheat.

### SUMMARY

Food allergy is a problem which concerns all physicians, and a more general knowledge of its nature is vital to the practice of medicine.

Food sensitization is either fixed (constant) or cyclic (decreases and increases with the incidence of the food in the diet).

Cyclic food allergy may be either primary, concomitant or thermal in type. There are three distinct phases to the cycle of food sensitization and each of these has definite clinical implications.

In the practical application of the cyclic concept, it must be borne in mind that the three phases may, but often do not, develop in a precise, consecutive manner as they do following complete elimination of a food and its subsequent reentry into the diet. Thus, the diagnostician should be on the alert for any of the three phases and will not necessarily expect their strict consequential development.

Patients must be evaluated as to their inherent degree of tolerance for foods. If this is high, restrictive diets are in order. If low, a diversified and rotating diet is better.

It is easy to destroy a patient's tolerance for foods. It is paramount that tolerance be retained for every food possible.

One is not allergic to foods unless such allergy can be demonstrated by a correctly performed food test and such reactions must be specific and constant.

Masked food allergies are a common source of error in diagnosis. They make it impossible to determine by history if foods are either agreeable or allergic for the individual. Studies to prove food allergy require individual tests. Such tests must be supported by diet records and by instruction sheets informing patients of the source and contacts with various foods.

## SUMARIO

La alergia alimenticia es un problema que toca a todos los médicos y se ve que es necesario obtener informaciones más diversas para la medicina general interna.

La sensibilización alimenticia o fijada, a saber: constante o ciclical, señaladamente: se aumenta o se disminuye con la incidencia de alimento en la dieta.

La alergia alimenticia ciclical puede ser del tipo primario, concomitante o termal.

Existen tres distintas fases en el ciclo de la sensibilización alimenticia, y cada una de ellas tiene una importancia clínica definitiva.

Los enfermos deben ser evaluados según el grado o condición de sus tolerancia a los alimentos. Si ésta es alta, las dietas limitadas están en regla. Si es baja, una dieta diversificada y alternativa o cambiante es mejor.

Es fácil destruir la tolerancia alimenticia del enfermo. Es de importancia que la tolerancia sea retenida o conservada para cada alimento, posible.

Un individuo no se llama alérgico a los alimentos al menos que tal alergia pueda ser demostrada por una prueba a los alimentos correctamente hecha, y al menos que tales reacciones sean específicas y constantes.

Las alergias alimenticias enmascaradas son las comunes causas de los errores en la diagnosis. Ellas son responsables de la causa por no poder determinar por la historia, si los alimentos son agradables o alérgicos para el individuo.

Se necesitan pruebas individuales para demostrar la existencia de la alergia alimenticia. Tales pruebas deben ser soportadas por recuerdos dietéticos y por informaciones por escrito, informando a los enfermos del origen y de los contactos con diversos alimentos.

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## PENICILLIN FOR THE PUBLIC

(Condensed from *Science News*, April 15, 1944)

Sufficient penicillin to treat all urgent civilian cases should be available in the near future according to Robert D. Coghill, Chief of the Fermentation Division of the U. S. Department of Agriculture.

The commercial production of penicillin has been increased over a hundredfold the past year. This has been greatly stimulated by the discovery by Dr. A. J. Moyer of the action of corn steeping liquor on the growth of the mold. The cost of 100,000 units of penicillin has been reduced from \$20.00 to \$3.25 and will undoubtedly go much lower. There are now twenty-one of these penicillin-producing fermentation plants being erected in this country and Canada. It is estimated that when completed, these plants will produce a sufficient amount of penicillin to treat approximately 250,000 serious cases per month. This will be the means of saving thousands of lives, to say nothing of arms and legs of our fighting men.

## SENSITIVITY TO MINOR POLLENS

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IN eastern Pennsylvania, any pollen other than ragweed or grass is a minor pollen. Relatively few persons are sensitive to them. Botanically, they differ from the major pollens because the season is shorter, the atmospheric concentration is much less, and is much more variable from year to year.

In early spring, the minor pollens come from trees. There is usually a week of high atmospheric concentration, but this is likely to vary greatly with the distance from a forest. In three years of differential atmospheric pollen counts, we have at no time seen any prolonged concentration such as is the rule with grass and ragweed. There are occasional peaks during which the count for one day may be much greater than is usually seen in ragweed and grass. The tree and grass seasons usually overlap.

During the grass season plantain and sheep sorrel appear. In spite of the fact that the plants continue to bloom throughout most of the summer, the pollen is found on the atmospheric slides for only about three weeks. The concentration on any particular day is never more than about 25 per cent of the grass and the total count for the season is also about 25 per cent of the grass. During the ragweed season *Chenopod* pollen appears but in concentration of only about 10 per cent of that of ragweed. Hops appears in somewhat greater concentration and deserves further study. Cocklebur and *Artemesia* are close relatives of ragweed, and the Prausnitz-Kustner bodies of the former are interchangeable with those of ragweed. It is probable that hyposensitization with ragweed will also give protection against its relatives.

Plantain has been a recognized cause of hayfever for many years. It was among the first of the minor pollens to be recognized and has been used as a routine skin test on all persons suffering from early summer hay fever. For these reasons it was chosen for a detailed study. It is thought that the facts obtained from this study will apply to all the minor pollens.

We have found 102 persons with positive skin reactions to plantain in private practice. These persons may be divided into six groups:

*Group 1.*—Those in whom the plantain is the primary and sole cause of hay fever. These persons had a history of about four weeks of hay fever, chiefly in the month of June. They all had strongly positive skin and eye reactions to plantain and entirely negative reactions to grass and tree pollens. They all responded to specific pollen treatment.

Only two of the present series come under this group, although two entirely similar cases were seen at the Jefferson clinic.

*Group 2.*—Another small group (five) whose season corresponded to the first group but who had a positive but very much weaker reaction to grass or tree pollen. In this group plantain may be regarded as the major



synergen and grass as the minor synergen. Unfortunately all but one of these persons were treated with a mixture of grass and plantain.

*Group 3.*—A much larger series in whom the grass reaction was equal to, or more often greater than, the plantain reaction. This group was composed of fifty-four persons. Eight were treated with grass alone for one or more seasons and then were treated with a mixture of grass and plantain. Six of these obtained a better result when the mixture was used than in the previous years when grass alone was used.

*Group 4.*—A group of sixteen in whom the plantain reaction was only one of a large number of positive skin reactions to pollens (chiefly the trees) appearing in the spring and early summer. In almost all, sorrel and grass were also positive.

Hay fever caused by pollen from a simple species of tree occurs but is as rare as that due to plantain alone. It responds very easily to specific treatment. It is much more common to find a positive reaction to four, five or more trees as well as reactions to plantain, sheep sorrel and grass pollen.

This group has been particularly difficult to treat. The worst period is the first two weeks in May. Our treatment has consisted in injections of two mixtures, the first containing those trees to which the person gives the strongest skin reactions and the second a mixture of grass and plantain and sorrel. In spite of these painstaking and elaborate preparations, the results are too often disappointing.

*Group 5.*—A small group of sixteen typical late hay fever (ragweed) sufferers who have what appears to be a relatively unimportant skin reaction to plantain. This group is not nearly so large as those with similar unimportant reaction to grass.

Most of these persons do not have any symptoms in the spring. A few have mild nasal irritation and were treated with a few phylactic doses of plantain. None had enough trouble to justify the usual prophylactic treatment.

*Group 6.*—Another small group of nine who came to us with serious allergic symptoms throughout the year. Three had no history of hay fever. Six had very mild hay fever, not sufficiently severe to justify treatment. We did give plantain injections to a few with apparently beneficial effect on the more serious symptoms. One of this group died in an acute asthmatic seizure.

The possibility of a cure after specific treatment is much greater in plantain sensitivity than it is in either grass or ragweed. Furthermore, diminution or disappearance of the skin reaction is the rule rather than the exception. In the present series, forty-three had a reasonably complete prophylactic course of plantain injections. In twenty-three the skin reaction was distinctly reduced the following spring and in two, it was rated as negative.

In one instance the skin reaction to plantain entirely disappeared after

## SENSITIVITY TO MINOR POLLENS—ROGERS

six years of specific treatment only to reappear and become clinically active after seven years. This was a woman forty-seven years of age who suffered from both early and late hay fever for twenty-five years. She was treated with both grass and plantain from 1929 to 1931, inclusive with an excellent result. In 1932 the skin reaction to plantain disappeared and she was treated with grass only from 1932 to 1936, inclusive. The result was excellent from 1932 to 1935 but only mediocre in 1936. The skin reaction to plantain became positive again in 1935. This year, however, she received grass treatment alone with only a fair result. In 1937 plantain was again added to the treatment and the former excellent result obtained.

Of the 102 who reacted to plantain, fifty-five also reacted positively to sheep sorrel. We have seen but one person who reacted to sorrel and not to either plantain or grass. This was a very weak reaction and was probably the cause of a very mild hay fever.

Another person had a much stronger reaction to sorrel than to grass. However, she had been receiving perennial treatment elsewhere with grass pollen with only mediocre results. She probably corresponds to our second group and the sorrel had acted as the major synergist. We believe that sorrel frequently acts as a minor synergist, particularly in those with the tree, grass or plantain reactions. When positive it should be added to the grass and plantain mixture.

Likewise, a simple tree as the sole cause of hay fever is rare but does occur. In our district, oak is most common, sycamore is next.

We had one woman with an unusually strong reaction to willow and only weak reactions to other pollens. Treatment was unusually successful and before her death from cancer, the skin reaction to willow had become completely negative.

Fifty-six reacted to ragweed. In twenty-two the reaction was of little importance, hay fever being absent or nearly so during August and September. Thirty-two, in addition to actual hay fever in the early summer, had sufficiently severe symptoms in the fall to justify treatment. It is interesting to note that all those in the fourth group (sixteen persons), with multiple tree reactions, had annoying symptoms from ragweed. In the fifth group (also sixteen persons) ragweed hay fever was the reason for consulting us and the reactions to spring pollens were unimportant.

Of the inhalants encountered throughout the year, there were eighty-one positive reactions to house dust, twenty-nine to orris root, seventeen to feathers, and eleven to animals. Thirty-one had minor nasal symptoms throughout the year, but only thirty-four had distressing symptoms.

Whenever a reaction to one of these year around substances was found, treatment was started immediately. This consisted in avoidance of the substance during the season and usually hyposensitization. House-dust extract was used in treatment in fifty-five and orris root in thirteen. We believe it is well worth the additional effort.

## CONCLUSIONS

In eastern Pennsylvania—

1. Pollens other than grass and ragweed are rarely the sole cause of hay fever.
2. They frequently complicate or act as minor synergens to the major pollens.
3. Treatment is more satisfactory than it is for the major pollens.
4. "Cures" and diminution in the intensity of the skin reaction are more common than in the major pollens.

## CONCLUSIONES

1. Otros pólenes, fuera de los de las Gramíneas y Malezas (Ambrósias), son raramente los únicos responsables de la fiebre de heno o polinosis.
2. Ellos frecuentemente hacen complicar o se conducen como sinérgenos menores a los pólenes principales o mayores.
3. El resultado del tratamiento es mucho más satisfactorio que en los pólenes principales.
4. En estos pólenes se encuentra, ordinariamente, más "curas" y disminución en la intensidad de la reacción cutánea, que en los pólenes principales.

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## A LETTER FROM THE FRONT\*

Dr. Alexander Altose wrote from the New York Port of Embarkation, January 22, 1944. . . . "You might be interested in my story and wanderings. Since last June, when I left California, I have traveled over 30,000 miles in every sort of conveyance from jeep to ship to transport plane. I spent a few weeks at the Station Hospital at Camp Kilmer, New Jersey, and there helped a bit in the Allergy Clinic. Since then, I have been to North Africa and to the British Isles. I have seen several countries, the best of which is, naturally, the good old U. S. A.

"I shall leave again in a few days for another voyage. My duties are those of a transport surgeon—a good job but a far cry from allergy. I do miss the allergy, as there is plenty of it to be done in the Army, but I do as I am told. There is a big job to be done overseas and fellows like myself must expedite it. Meanwhile, you allergists at home will keep the field active and thus help give us something to which to return.

"I hope to resume contact with my books and journals this Spring and am anxious to read the back issues of THE ANNALS."

---

\*Letters are welcome from those in the service. Please send more of them.

# P R E L I M I N A R Y   P R O G R A M

## First Annual Meeting *American College of Allergists*

June 10 and 11, 1944

Palmer House  
Chicago, Illinois



95th Annual Meeting, American Medical Association, Palmer House,  
Chicago, June 12-16, 1944

10th Annual Meeting, American College of Chest Physicians, Stevens  
Hotel, Chicago, June 10-12, 1944

NOTE: The papers will not necessarily be presented in the order indicated  
in this preliminary program and the titles of the papers and authors are  
also subject to change.



—*Photograph by Fabian Bachrach*

SANFORD BURTON HOOKER, M.D.

*Boston, Massachusetts*

Guest Speaker, 1944

# Preliminary Program

Saturday, June 10, 1944

## Breakfast

(Place to be announced)—7:30 to 8:30 a.m.

Members of Board of Regents and Program Committee

## Registration

Fourth Floor—8:00 a.m.

## Instructional Courses

Club Floor—8:30 to 10:30 a.m.

Otorhinolaryngologic Allergy—FRENCH K. HANSEL, M.D., St. Louis, Missouri (Room 14)

Pediatric Allergy—JEROME GLASER, M.D., Rochester, New York; CHARLES S. MILLER, M.D., Corona, New York (By invitation); MARION B. SULZBERGER, Commander (MC) USNR, New York, New York (By invitation); RALPH BOWEN, M.D., Houston, Texas (Room 18)

Gastro-Intestinal Allergy—ORVAL R. WITHERS, M.D., Kansas City, Missouri (Rooms 15 and 16)

Allergy of the Central Nervous System—T. WOOD CLARKE, M.D., Utica, New York, and J. WARRICK THOMAS, M.D., Cleveland, Ohio (Room 17)

## Symposium on Service Allergy

Red Lacquer Room—10:30 a.m. to 1:00 p.m.

Allergy in the Army—COLONEL SANFORD W. FRENCH, (MC) USA, 4th Corps Command, Atlanta, Georgia, and MAJOR LAWRENCE T. HALPIN, (MC) AUS, 4th Corps Command, Atlanta, Georgia

*Commentator:* LT. COL. L. E. LIEDER, Army Service Forces, Walter Reed General Hospital, Washington, D. C.

Allergic Dermatoses in the U. S. Navy—COMMANDER MARION SULZBERGER, (MC) USNR, New York, N. Y. (By invitation)

*Commentator:* LT. MORRIS LIEDER, (MC) USNR, Dispensary, U. S. Naval Air Station, Pensacola, Florida (By invitation)

Allergic Dermatitis in War Industries—LOUIS SCHWARTZ, M.D., Medical Director, U. S. Public Health Service, Bethesda, Maryland

*Commentator:* SAMUEL M. PECK, M.D., Senior Surgeon, U. S. Public Health Service, Bethesda, Maryland (By invitation)

## College Luncheon

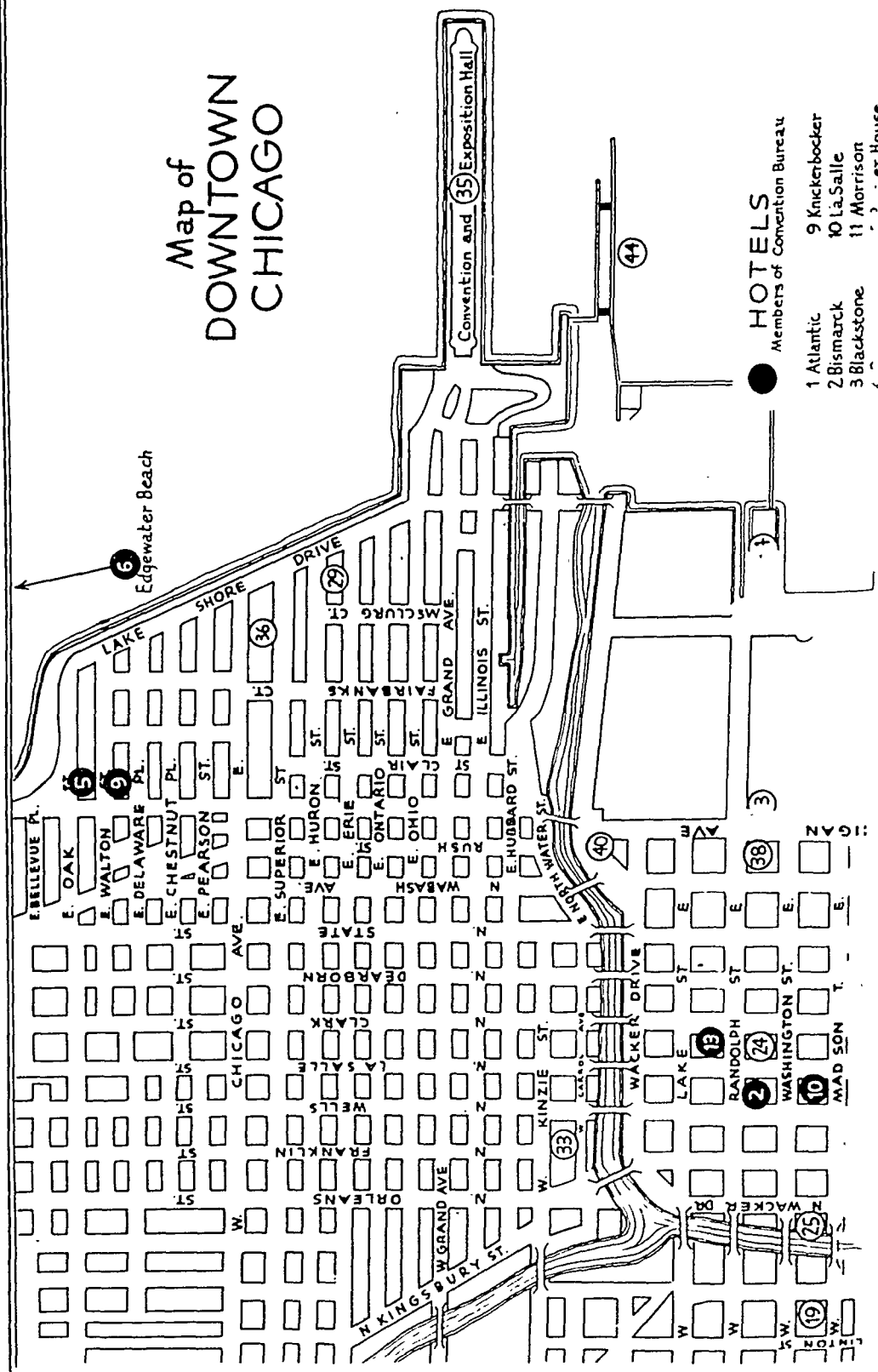
Red Lacquer Room—1:00 to 2:00 p.m.

## The Physiologic, Pathologic and Immunologic Aspects of Allergy

Red Lacquer Room—2:00 to 5:00 p.m.

Address of the Guest of Honor: Qualitative Differences in Canine Dander—SANFORD B. HOOKER, M.D., Boston University, Boston, Massachusetts

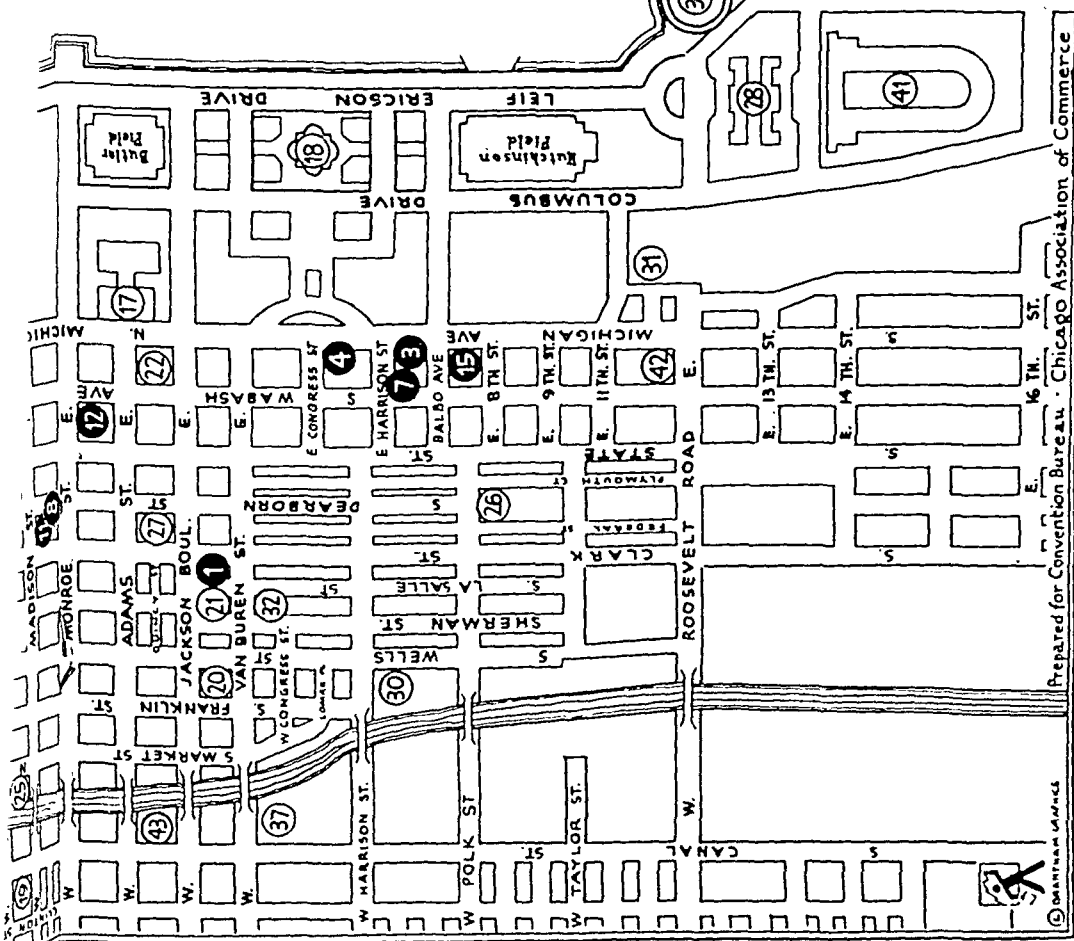
# Map of DOWNTOWN CHICAGO



- 5 Drake  
6 Edgewater Beach  
7 Harrison  
8 Hamilton  
13 Sherman  
14 Shoreland  
15 Stevens

# POINTS OF INTEREST

- 16 Adler Planetarium  
17 Art Institute  
18 Buckingham Fountain  
19 Chicago & Northwestern Station  
20 Chicago, Aurora & Elgin Station  
21 Chicago Board of Trade Building  
(Observation Tower)  
22 Chicago, North Shore & Milwaukee Sta.  
23 Chicago, South Shore & South Bend Sta.  
24 City Hall & County Building  
25 Civic Opera Building  
26 Dearborn Street Station  
27 Federal Building  
28 Field Museum  
29 Furniture Mart  
30 Grand Central Station  
31 Illinois Central Station  
32 La Salle Street Station  
33 Merchandise Mart  
34 Naval Armory  
35 Navy Pier  
36 Northwestern University  
(Chicago Campus)  
37 Post Office  
38 Public Library  
39 Shedd Aquarium  
40 Site of original fort Dearborn  
41 Soldier Field  
42 Union Bus Station  
43 Union Station  
44 Chicago River Controlling Works





## PRELIMINARY PROGRAM

- Dermatologic Manifestations of Familial Nonreaginic Food Allergy—ARTHUR F. COCA, M.D., Pearl River, New York
- Physiologic Aspects of Allergy—CHARLES F. CODE, M.D., Mayo Clinic, Rochester, Minnesota (By invitation)
- The Mechanism of Desensitization—J. BRONFENBRENNER, Ph.D., Washington University, St. Louis, Missouri (By invitation)
- Immunologic Studies of Hay Fever—MARY H. LOVELESS, M.D., New York, New York (By invitation)
- The Aerobiologic Phase of Allergy—E. C. STAKMAN, Ph.D., Chief of Division of Plant Pathology and Botany, Department of Agriculture, University of Minnesota, Saint Paul, Minnesota

### Almay Cocktail Hour

*Place to be announced—7:00 to 8:00 p.m.*

Presented through the courtesy of Almay, Inc., New York, N. Y.

### Informal Dinner

*Red Lacquer Room—8:00 p.m.*

Address of the President—FRENCH K. HANSEL, M.D., St. Louis, Missouri  
Symphony of the Seasons (Motion picture with color and sound—symphony music)  
—HERBERT J. RINKEL, M.D., Kansas City, Missouri

## Sunday, June 11, 1944

### Breakfast

*(Place to be announced)—7:30 to 8:30 a.m.*

Members of Board of Regents and Program Committee

### Registration

*Fourth Floor—8:00 a.m.*

### Instructional Courses

*Club Floor—8:30 to 10:30 a.m.*

- Dermatologic Allergy—LOUIS A. BRUNSTING, M.D., Rochester, Minnesota (Room 18)
- Asthma—LEON UNGER, M.D., Chicago, Illinois (Room 14)
- Drug Allergies—ETHAN ALLAN BROWN, M.D., Boston, Massachusetts (Rooms 15 and 16)

### Scientific Progress in Allergy

*Red Lacquer Room—10:30 a.m. to 1:00 p.m.*

- Chronic Urticaria in Female Castrates—CARL J. DEISSLER, M.D., San Francisco, California
- Observations on Several Hundred Cases of Asthma Observed in the Station Hospital, Allergy Clinic, Fort Bliss—BERTHOLD N. STERN, *Captain* (MC), AUS, Ft. Bliss, Texas

## PRELIMINARY PROGRAM

- A Method for the More Accurate Estimation of the Importance of Individual Plant Species Concerned in Pollinosis—GEORGE F. HARSH, Lt. Comdr. (MC) USNR, San Diego, California, MRS. HELEN McMICHAEL, R.N., and MRS. JULIA KLEIN, R.N., San Diego, California
- Problems in the Diagnosis of Asthma—GEORGE L. WALDBOTT, M.D., Detroit, Michigan
- Chemical Evaluation of Soybean Milk and Oil in Allergic Infants and Children—ALBERT V. STOESEER, M.D., University of Minnesota Medical School, Minneapolis, Minnesota
- The Allergy Problem of the Inductee, the Soldier and the Veteran—HENRY I. SHAHON, Captain (MC) AUS, Veterans Administration Facility, First Service Command Unit, West Roxbury, Massachusetts
- Unusual Complications of Bronchial Asthma: Air in Extrapulmonary Areas—V. J. DERBES, M.D., Tulane Medical School, New Orleans, Louisiana
- Growth and Development of Allergic Diseases. A Study of 100 Allergic Children from Infancy to Ten Years of Age—NORMAN W. CLEIN, M.D., Seattle, Washington
- Serum Potassium Response to Epinephrine in Normal and Asthmatic Subjects—SUSAN C. DEES, M.D., Duke University, Durham, North Carolina
- Pollinosis and Other Problems in the Practice of Allergy in Mexico—MARIO SALAZAR MALLÉN, M.D., Mexico City, Mexico
- A New Technique for the Indirect Method of Skin Testing—ROBERT S. McGRATH, M.D., Washington, D. C.  
*(Papers limited to 15 and 20 minutes)*

## RECESS

### Committee Meetings

*Place to be announced—2:00 to 3:00 p.m.*

### Board of Directors and Board of Regents

*Place to be announced—3:00 to 4:00 p.m.*

### Annual Business Meeting

*Red Lacquer Room—4:00 to 5:00 p.m.*

Election of Officers—Committee Reports

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## PROPOSED SECTION OF VETERINARY ALLERGISTS

### Organization Meeting

**Friday, June 9, 1944**

*Room 17, Club Floor—2 to 5 p.m.*

- Introductory Remarks—I. FOREST HUDDLESON, D.V.M., Lansing, Michigan
- Classification of the Phenomena of Specific Sensitivity in Lower Animals—CHARLES ROBBINS SCHROEDER, D.V.M., Pearl River, New York
- Reaginic Allergy in Cattle—LESTER REDDIN, JR., D.V.M., Pearl River, New York
- Allergy in the Dog—Allergic Rhinitis, Dermatitis and Urticaria (Illustrated by slides and colored film)—FRED W. WITTICH, M.D., and F. W. GEHRMAN, D.V.M., Minneapolis, Minnesota
- Serum Sickness in Rabbits—MOYER S. FLEISHER, M.D., St. Louis, Missouri  
*Discussions will be welcomed*

PRELIMINARY PROGRAM

SCHEDULE OF COURSES

Saturday, June 10, 1944

Palmer House

8:30 to 10:30 A.M.

\$2.00 per course

**Course A-1 PEDIATRIC ALLERGY**—Room 18, Club Floor

JEROME GLASER, M.D., Rochester, N. Y.; CHARLES S. MILLER, M.D., Corona, N. Y. (By invitation); MARION B. SULZBERGER, Cdr. (MC) USNR, New York, N. Y. (By invitation); RALPH BOWEN, M.D., Houston, Texas

**Course A-2 OTORHINOLARYNGOLOGIC ALLERGY**—Room 14, Club Floor

FRENCH K. HANSEL, M.D., St. Louis, Missouri

**Course A-3 GASTRO-INTESTINAL ALLERGY**—Rooms 15 and 16, Club Floor

ORVAL R. WITHERS, M.D., Kansas City, Missouri

**Course A-4 ALLERGY OF THE CENTRAL NERVOUS SYSTEM**—Room 17, Club Floor

T. WOOD CLARKE, M.D., Utica, New York, and J. WARRICK THOMAS, M.D., Cleveland, Ohio

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Sunday, June 11, 1944

Palmer House

8:30 to 10:30 A.M.

\$2.00 per course

**Course B-5 DERMATOLOGIC ALLERGY**—Room 18, Club Floor

LOUIS A. BRUNSTING, M.D., Mayo Clinic, Rochester, Minnesota

**Course B-6 ASTHMA**—Room 14, Club Floor

LEON UNGER, M.D., Chicago, Illinois

**Course B-7 DRUG ALLERGIES**—Rooms 15 and 16, Club Floor

ETHAN ALLAN BROWN, M.D., Boston, Massachusetts

**Section on Instruction**  
**ADVANCE ORDER SHEET**

All courses cost \$1.00 for each hour. By following explicitly the instructions and by listing the exact courses desired, errors will be minimized.

**RECAPITULATION OF GENERAL INSTRUCTIONS**

- (1) Saturday, June 10, 1944, 8:30 a.m. to 10:30 a.m., represented by Key A-1, A-2, A-3, A-4.
- (2) Sunday, June 11, 1944, 8:30 a.m. to 10:30 a.m., represented by Key B-1, B-2, B-3
- (3) Members ONLY having paid 1944 dues may reserve conference tickets by mail

**PREVIOUS TO JUNE 7, 1944**

Send order to:

FRED W. WITTICH, M.D., *Secretary-Treasurer*  
401 La Salle Medical Bldg.  
Minneapolis 2, Minnesota

**AFTER JUNE 7, 1944**

Mail to:

FRED W. WITTICH, M.D.  
Palmer House  
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College Candidates and Nonmembers May Purchase Tickets at Registration  
Desk ONLY

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The following information is essential. Please check the proper squares.

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☐ Honorary

☐ Active

☐ Associate

Money enclosed \$.....

(over)

- (4) After June 10, no distinction will be made between members, candidates or nonmembers in filling orders
- (5) Candidates and nonmembers will make selection for courses at the General Registration Desk in Chicago—ONLY
- (6) All candidates, nonmembers and members will be required to pay a fee when registering to attend the convention.

In designating courses, list instructor's name once only. If assignment of period specified is not possible, an attempt will be made to re-arrange schedule to include "second choice." Seven courses will be given of two hours each—four on Saturday morning and three on Sunday morning—thus, two courses will be available to each registrant.

<i>Saturday, June 10, 1944</i>	<i>Sunday, June 11, 1944</i>
<p style="text-align: center;"><b>First Choice</b></p> <p>Course No.            Lecturer:</p>	<p style="text-align: center;"><b>First Choice</b></p> <p>Course No.            Lecturer:</p>
<p style="text-align: center;"><b>Second Choice</b></p> <p>Course No.            Lecturer:</p>	<p style="text-align: center;"><b>Second Choice</b></p> <p>Course No.            Lecturer:</p>
<p style="text-align: center;"><b>Third Choice</b></p> <p>Course No.            Lecturer:</p>	<p style="text-align: center;"><b>Third Choice</b></p> <p>Course No.            Lecturer:</p>
<p style="text-align: center;"><b>Fourth Choice</b></p> <p>Course No.            Lecturer:</p>	

**Do Not Make Notations Here**

**This Space for Secretary's Use for Tickets Allotted**

<b>Saturday A-1</b>	<b>Sunday B-1</b>
<p>"    <b>A-2</b></p>	<p>"    <b>B-2</b></p>
<p>"    <b>A-3</b></p>	<p>"    <b>B-3</b></p>
<p>"    <b>A-4</b></p>	

## THE MOLAR STANDARDIZATION OF RAGWEED POLLEN EXTRACTS

GEORGE E. ROCKWELL, M.D., F.A.C.A.

Cincinnati, Ohio

NUMEROUS methods such as Noon unit,<sup>15</sup> dilution of extract used,<sup>20</sup> total nitrogen,<sup>10,12</sup> so-called protein nitrogen unit,<sup>11,13,14</sup> (phosphotungstic acid precipitate nitrogen), and serological reactions,<sup>3,4,5,8,9,21</sup> have been used for standardizing pollen extracts. However, none of these methods are entirely satisfactory as it has been practically impossible to prepare different extracts of pollen which are clinically interchangeable.

Standardizing solutions on a chemical basis may be done in several ways, namely, as normal solutions, as molar solutions, or on their oxidizing or reducing capacities. Standardization of pollen extract by one of these chemical methods would be scientifically accurate and would make it possible to reduplicate or interchange extracts. However, ragweed pollen extract contains more than one antigen; therefore, standardization on the molar basis would involve the standardization of a solution containing a mixture of substances. Under certain conditions this is feasible and accurate providing certain information concerning the composition of the substances is known.

With this in mind let us review the chemical composition of the ragweed pollen antigen. In previous papers<sup>16,17,18</sup> we have shown that the major antigen in ragweed pollen extract has a molecular weight of 4496, and each molecule contains thirty-eight nitrogen atoms of which two are free  $\alpha$ -amino nitrogen atoms. In addition to this major antigen we have shown that there are four lesser antigens with molecular weights of 1,000 or thereabouts. These low molecular weight antigens contain from two to nine nitrogen atoms per molecule of which one is a free  $\alpha$ -amino nitrogen atom. These findings are in keeping with those reported by Abramson<sup>1,2</sup> who described a major antigen having a molecular weight of approximately 5,000 and several pigmented minor antigens having much lower molecular weights.

In Table I are listed the more important chemical data concerning the antigens found in crude ragweed pollen extract. From this table we note that the molecular weight of the major antigen, Fraction 1, is over four times greater than the average molecular weight of the four minor fractions. From the column in Table I designated "No. of Nitrogen Atoms per Molecule," it is readily seen that there is an appreciable difference between the various fractions; Fraction 1 containing approximately 65 per cent of the total nitrogen with the remaining 35 per cent being distributed among the lesser antigens. From the column "No. of Free  $\alpha$ -Amino Groups per Molecule" the unique distribution is at once noted, namely that Fraction 1 contains two free  $\alpha$ -amino groups per molecule

# RAGWEED POLLEN EXTRACTS—ROCKWELL

TABLE I. A SUMMARY OF THE CHEMICAL NATURE OF THE VARIOUS FRACTIONS OF RAGWEED POLLEN EXTRACT.

Fraction	Molecular Weight	No. Flavonol Radicals in Each Molecule	No. Amino Acids Per Molecule	No. Nitrogen Atoms Per Molecule	No. of Free A-Amino Groups Per Molecule	Per Cent of Total Nitrogen Which is Free A-Amino Nitrogen
1	4496	1	28	38	2	5.26
2	1096	1	6	6	1	16.66
3	951	1	3	3	1	33.33
4	651	1	2	2	1	50.00
5	1123	1	4	9	1	11.11

while the lesser antigens each contain only one free a-amino group per molecule.

Thus, we find two main groups of antigens in ragweed pollen extract: Group A (Fraction 1) which has a high molecular weight and contains a large number of nitrogen atoms per molecule of which two are free a-amino groups; and Group B (minor antigens) which has an average molecular weight of approximately 1,000 and contains a small number of nitrogen atoms of which only one is a free a-amino group per molecule. Because the big immunological differences are between Groups A and B rather than between the members of Group B, it is feasible and practical for our present purposes to consider these antigens in the two groups. Table II shows the data of Table I rearranged on this basis. From Table II it can readily be seen that by determining the total amount of nitrogen and the total free a-amino nitrogen in the active antigen in the pollen extract any of the data in Tables I or II can be computed.

The phosphotungstic acid precipitate is a convenient and practical method of separating the active antigen from the crude extract. Cooke recognized this when he proposed the so-called protein nitrogen unit. However, Brown and Benotti<sup>7</sup> state that the removal of the phosphotungstic acid precipitate does not entirely remove the skin-test-reactive material from the supernatant fluid. In concentrated extracts after the complete removal of the phosphotungstic acid precipitate (with the aid of thorough chilling after the reaction has been completed), we have found that if the remaining phosphotungstic acid is removed from the supernatant fluid by repeated extraction with ether and the excess acid neutralized, then the supernatant fluid contains less than 2 per cent of its original concentration of skin-reactive material. Although the phosphotungstic acid precipitate of ragweed pollen extracts may not absolutely represent the active pollen antigen, it still is the most convenient and

# RAGWEED POLLEN EXTRACTS—ROCKWELL

TABLE II. SHOWING IMPORTANT COMPONENTS OF THE TWO GROUPS OF ANTIGENS IN RAGWEED POLLEN EXTRACT.

Group	Molecular Weight	Total Nitrogen Atoms Per Molecule	No. of Free A-Amino Nitrogen Atoms per Molecule	Per Cent of Total Nitrogen Which is Free A-Amino Nitrogen
A (Frac. 1)	4496	38	2 (A)	5.26
B average	955	5	1	20.00
1 Mol. A & 4 Mols. B		58 (T)	6 (X)	10.345

practical method available. Therefore, we have used this method in the following experiments for obtaining the total and the free a-amino nitrogen of the active antigen.

## *Calculation of Distribution of the Free A-Amino Nitrogen—*

Where

T=total nitrogen of both A and B (PTA ppt. nit.)

X=total free a-amino nitrogen of both A and B (free a-amino nit. of PTA ppt.)

A=amount of free a-amino nitrogen in Group A (Fraction 1)

B=amount of free a-amino nitrogen in Group B

then

$$A = 0.3568T \left( 0.2 - \frac{X}{T} \right)$$

and

$$B = X - A$$

From the above equations we are able to determine the amount of free a-amino nitrogen in the extract which represents Group A (Fraction 1) and Group B. If desired on a similar basis and without additional determinations, Fractions 2, 3, 4, and 5 can be calculated. However, for purposes of standardization in molar solution the important consideration is how much of the extract is major antigen and how much is minor antigen.

*Calculation of Molar Concentration.*—Group A (Fraction 1): Knowing the amount of free a-amino nitrogen in the extract which is due to Fraction 1 we can calculate its molar concentration since we know that each molecule contains 2 free a-amino nitrogens. Thus, a one molar solution would contain 28.016 grams of free a-amino nitrogen per liter or 28.016 mgs. per ml.



Hence where

A=amount of free a-amino nitrogen in Group A  
then

$$AM \text{ (Fraction 1 Molar Concentration)} = \frac{A}{28.016}$$

and for Group B, since it contains only 1 free a-amino group per molecule

$$BM \text{ (Group B Molar Concentration)} = \frac{B}{14.008}$$

$$TM \text{ (Total Molar Concentration)} = AM + BM$$

*Calculation for Converting to Molar Units.*—But such molar expression would be confusing to the allergist who is used to units or dilutions, therefore, we have converted the above to molar units.

For convenience a new unit chosen should approximate a unit now used for standardization, hence we have selected a Molar Unit which is almost equivalent to a Noon Unit, namely 1 ml of a  $4 \times 10^{-8}$  molar solution; thus:

$$AMU \text{ (Fraction 1 Molar Units)} = \frac{AM}{4 \times 10^{-8}}$$

$$BMU \text{ (Group B Molar Units)} = \frac{BM}{4 \times 10^{-8}}$$

$$TMU \text{ (Total Molar Units)} = AMU + BMU$$

Combining these equations with those given under "Calculation of molar concentration" we have:

$$\begin{aligned} AMU &= 892,000.A \\ BMU &= 1,785,000.B \\ TMU &= AMU + BMU \end{aligned}$$

*Résumé of Determinations and Calculations Necessary for Molar Standardization.*†—Thus in the molar standardization of ragweed pollen extract it is only necessary to make two determinations:

- (1) Total nitrogen in PTA ppt.=T
- (2) Free a-amino nitrogen in PTA ppt.=X

and use the following equations:

$$(1) A = 0.3568T \left( 0.2 - \frac{X}{T} \right)$$

$$\begin{aligned} B &= X - A \\ (2) AMU &= 892,000.A \\ BMU &= 1,785,000.B \\ TMU &= AMU + BMU \end{aligned}$$

#### EXPERIMENTAL

*Method.*—The phosphotungstic acid precipitate was prepared by taking an aliquot amount of the extract (3 to 10 ml. depending upon the concentration of the extract) to which was added sufficient concentrated HCl to give a final concentration of 10 per cent and sufficient phosphotungstic acid solution to give a final concentration of 5 per cent. This

†If a purified extract which contains only the active antigen (such as prepared by Efron's, Rockwell's, or other methods) is used then T, the total nitrogen, and X, the free a-amino nitrogen, should be determined directly on the purified extract and not on the phosphotungstic acid precipitate.

## RAGWEED POLLEN EXTRACTS—ROCKWELL

mixture was allowed to stand at room temperature until the reaction was complete and then placed in the ice box at 0° C. until thoroughly chilled (for best results this requires forty-eight hours). The precipitate was separated by centrifuging, and then carefully washed twice with 4 ml. portions of cold, ammonia-free water (preferably containing the same amount of HCl and phosphotungstic acid as the original mixture). This is essentially the method described by Block<sup>6</sup> for precipitation of basic amino acids.

The total nitrogen was determined by the micro Kjeldahl method and the free  $\alpha$ -amino nitrogen by the Van Slyke Manometric method.

*Analysis of Extract 1.*—(Extract of an equal mixture of large and small ragweed pollen.) This analysis is given with details of calculations in order to illustrate standardization as molar units.

T (total nitrogen in PTA ppt.) = 0.4188 mg. per ml.

X (free  $\alpha$ -amino nitrogen in PTA ppt.) = 0.05875 mg. per ml.

then since

$$A = 0.3568T \left(0.2 - \frac{X}{T}\right)$$

$$A = 0.3568 \times 0.4188 \left(0.2 - \frac{0.05875}{0.4188}\right)$$

$$A = 0.00887$$

$$B = X - A = 0.05875 - 0.00887 = 0.0499$$

then

$$AMU = 892,000 \times 0.00887 = 7,912$$

$$BMU = 1,785,000 \times 0.0499 = 89,071$$

$$TMU = 7,912 + 89,071 = 96,983$$

Total nitrogen in Fraction 1 = 0.1686 mg. per ml.  
or 40.23 per cent of total nitrogen in PTA ppt.

Total nitrogen in Group B = 0.2495 mg. per ml.  
or 59.77 per cent of total nitrogen in PTA ppt.

Extracts of pollen differ not only with the sample of pollen but with its age, type of extracting fluid used, concentration of the extraction, reaction of the extracting fluid, and probably many other factors. This variation is not only in the actual amount of antigen extracted but also an even larger variation in the distribution of the antigens between Fraction 1 (large molecule) and Group B (small molecule). To illustrate this the analysis of another equal mixture of ragweed pollen extract is given below.

*Analysis of Extract 2.*—

T (total nitrogen in PTA ppt.) = 0.460 mg. per ml.

X (free  $\alpha$ -amino nitrogen in PTA ppt.) = 0.0465 mg. per ml.

therefore

$$A = 0.0163$$

$$B = 0.0302$$

$$AMU = 14,539$$

$$BMU = 53,907$$

$$TMU = 68,446$$

Total nitrogen in Fraction 1 = 0.309 mg. per ml.  
or 67.17 per cent of the total nitrogen in the PTA ppt.

Total nitrogen in Group B = 0.151 mg. per ml.  
or 32.83 per cent of the total nitrogen in the PTA ppt.

In comparing the two extracts it will be noted that the total nitrogen is a little higher in Extract 2 and hence the so-called protein nitrogen units would be higher. On the converse, Extract 2 contains almost 50 per cent fewer total molar units (TMU) than Extract 1, but 100 per cent more Fraction 1 molar units (AMU) than Extract 1. In Extract 2, Fraction 1 contains 67.17 per cent of the total nitrogen whereas in Extract 1 it is only 40.23 per cent. This is shown in Figure 1.

These differences clearly depict the reasons why standardization by present methods is not satisfactory; also they clearly illustrate the value and importance of molar standardization in which the number of large molecules and the number of small molecules are considered. To further demonstrate this the pollen from a previous experiment was reextracted. According to Roth and Nelson<sup>19</sup> this second extraction should contain fewer large molecules in proportion to the number of small molecules than the first extract. If standardization in molar units is accurate then standardization of this extract (Extract 3 made by re-extracting the pollen from a previous experiment) should show a marked decrease in Fraction 1 molar units (AMU) as compared to Group B molar units (BMU).

*Analysis of Extract 3.*—(Extract obtained from the reextraction of pollen previously used)

T (total nitrogen in PTA ppt.) = 0.1200 mg. per ml.

X (free  $\alpha$ -amino nitrogen in PTA ppt.) = 0.0202 mg. per ml.

therefore

A = 0.00136

B = 0.01884

AMU = 1,213

BMU = 33,629

TMU = 34,842

Total nitrogen in Fraction 1 = 0.0258 mg. per ml.

or 21.50 per cent of the total nitrogen in the PTA ppt.

Total nitrogen in Group B = 0.0942 mg. per ml.

or 78.50 per cent of the total nitrogen in the PTA ppt.

From the analysis of Extract 3 it is quite evident that the second extraction of pollen contains much less Fraction 1 molar units (large molar units) than does the first extract and in proportion contains a much larger amount of small molar units. This not only verifies Roth and Nelson's previous observations but also checks the accuracy of standardization in molar units.

#### DISCUSSION

Molar standardization of pollen extract is simple and scientifically accurate; it should prove practical and useful in clinical application. It is important that pollen extracts be standardized as soon as possible after their preparation as the free  $\alpha$ -amino nitrogen changes with the aging of the extract although there may be no change in the total nitrogen or the phosphotungstic acid precipitate nitrogen. In fact, the aging of an extract can be followed by a study of its free  $\alpha$ -amino nitrogen.

## RAGWEED POLLEN EXTRACTS—ROCKWELL

The real value of molar standardization can only be shown by extensive clinical use of it; for this reason it is hoped that many clinicians will try this method. The writer will be glad to cooperate with any allergists wishing to use this method of standardization.

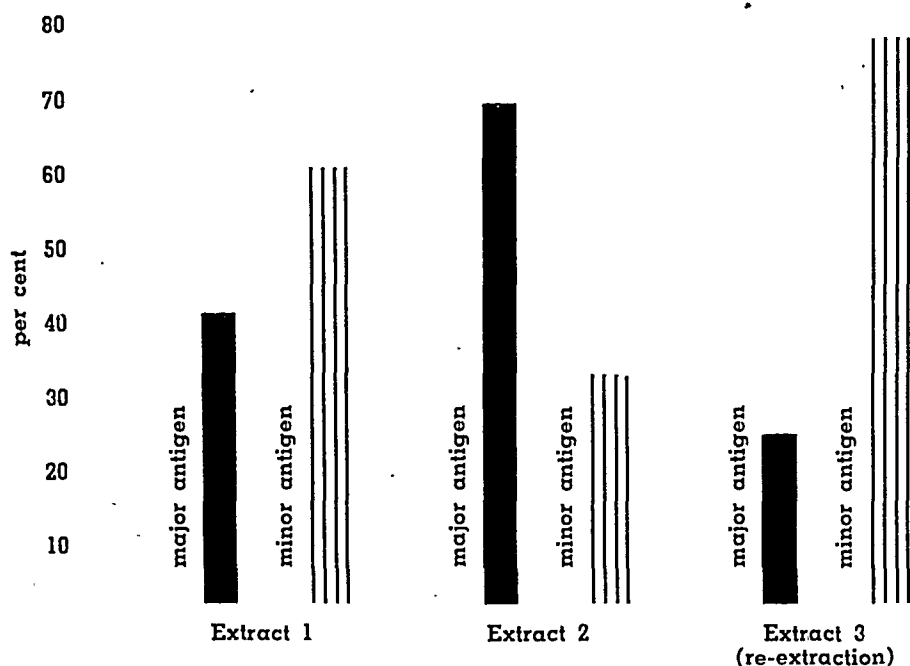


Fig. 1. Showing the percentage of total nitrogen in the phosphotungstic acid precipitate which is Major Antigen (Fraction 1) and Minor Antigen (Group B) in the various extracts.

### SUMMARY

1. A method is described for the standardization of pollen extracts as molar solutions.

2. To make these molar standardizations more practical for clinical use a formula is given for the conversion of molar concentration to molar units.

3. For standardization as molar units only two determinations are necessary, total nitrogen and total free  $\alpha$ -amino nitrogen in the phosphotungstic acid precipitate.

4. Sample analyses are given which not only illustrate exactly the standardization of pollen extract as molar units, but which also show graphically why standardization on the so-called protein nitrogen units, total nitrogen, dilutions used, or Noon Units, is unsatisfactory; and how standardization as molar units obviates these objections.

5. By studying the free  $\alpha$ -amino nitrogen it is possible to follow the aging of pollen extracts.

6. By molar standardization it is possible to detect differences in extracts which heretofore were not apparent.

The author expresses his appreciation to Phyllis Mugavin Rohrer, whose untiring devotion to the duties of the day made this work possible.

## RAGWEED POLLEN EXTRACTS—ROCKWELL

### SUMARIO

1. Se describe un método para la standardización de extractos de polen como soluciones molares.
2. Para hacer esta standardización molar mas práctica, para uso clínico se dá una fórmula para la conversión de concentración molar a unidades molares.
3. Para standardización como unidades molares, son necesarias dos determinaciones unicamente, nitrógeno total y nitrógeno a-amino libre total en el ácido fosfotungstico precipitado.
4. Se dan pruebas de análisis las cuales no solamente ilustran exactamente la standardización de extracto de polen como unidades molares, sino que tambien muestran graficamente porque standardización en el llamado unidades nitrógeno proteína, nitrógeno total, diluciones usadas o Unidades Noon, no es satisfactorio, y como standardización como unidades molares salva estas objeciones.
5. Por medio del estudio del nitrógeno a-amino es posible seguir el tiempo de envejecimiento de extractos de polen.
6. Por medio de la standardización molar es posible hallar diferencias en extractos, las cuales antes no eran aparentes.

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(Continued on Page 149)

## STERILE ABSCESS COMPLICATING ALUM-PRECIPITATED TETANUS TOXOID

### A Case Report

ARNOLD J. RAWSON, Assistant Surgeon, (R), U.S.P.H.S.

ALTHOUGH it is generally believed that sterile abscess is a not-too-rare reaction to alum-precipitated tetanus toxoid, a search of the literature by the author revealed a report on this subject by but a single group of authors.<sup>4</sup>

Literature on the reactions produced by tetanus toxoid is distinctly meager as compared with the number of reports on the subject of reactions to diphtheria toxoid. A discussion of the latter will therefore be included in this paper for the purpose of filling in gaps in our experience with the former.

Reactions to toxoid (diphtheria or tetanus) consist of two major types, general and local. It is not the purpose of this paper to discuss the general reaction, but in brief it consists of fever, chills, dizziness, headache, vomiting, diarrhea, muscular aches, and occasionally is accompanied by urticaria or anaphylaxis. It is generally believed that the general reaction is caused by the protein fraction of the toxoid, particularly by the Witte peptone in which the organism is grown.<sup>15</sup> This is particularly true of the definitely anaphylactic type of response. There is, indeed, evidence that the vast majority of reactions, both general and local, are due to previous sensitization to some part of the protein fraction of the toxoid. In a series of 949 cases receiving their first injection, Landes,<sup>9</sup> using fluid toxoid, reported no reactions. In a second series of mixed cases, he reported twelve reactions. Ten of these reacting patients had been previously injected. Similarly, Fulton<sup>3</sup> reports that local reactions are much more common in the Schick-negative than in the Schick-positive group, the former giving 86 per cent of reactions, the latter giving 42 per cent.

The local reaction consists of redness, induration, edema, pain, tenderness, and heat at and about the injection site. It may be accompanied by local lymphadenitis and occasionally by lymphangitis. The local reaction usually subsides completely in a few days, leaving no trace. Occasionally, however, the process goes on to suppuration with the formation of a sterile abscess. It is with this latter complication that this paper is principally concerned.

Sterile abscess occurs far more commonly with diphtheria toxoid than with tetanus toxoid. All cases reported have been found where alum-precipitated toxoid was used. The author has been unable to find any reports of sterile abscess following the use of formolized toxoid. Local reactions, as a whole, are far more severe following the alum-precipitated toxoid than they are following the formolized preparation.<sup>11</sup> A review of the literature reveals a report of two cases of sterile abscess in a series of 500 cases immunized with alum-precipitated tetanus toxoid by Gallagher et al.<sup>4</sup> No other paper reviewed by the author mentions this compli-

cation.<sup>2,5,7,8,12,13</sup> Numerous authors working with alum-precipitated diphtheria toxoid have encountered sterile abscesses, however. Harrison,<sup>6</sup> McGinnes,<sup>10</sup> and Fulton,<sup>3</sup> each report personal experience with this type of reaction, and the latter two quote instances of numerous cases of sterile abscess following the use of certain batches of toxoid. Personal communications<sup>1,14</sup> confirm the fact that a great number of sterile abscesses were encountered when alum-precipitated toxoid was first developed, and an excessive amount of alum was present in the product. Since the alum content was limited to 2 per cent, however, sterile abscesses have become rare. Sterile abscess, formerly produced in large number by improperly prepared toxoid, has now become a sign of individual idiosyncrasy.

It is known that superficial injection of alum-precipitated toxoid may frequently cause abscess formation. In fact, it is said that an abscess will almost invariably follow intracutaneous administration.<sup>1</sup> In this discussion, however, deep subcutaneous administration is the only type considered.

The local reactions occurring after the use of alum-precipitated toxoid may be caused either by the protein fraction as in the similar reactions following formolized toxoid, or else by the alum itself, or lastly by the combination of both, the precipitate acting as a mechanical device to hold the irritating protein products in contact with the tissue in concentrated form.<sup>6</sup> As mentioned previously, excessive alum was formerly a cause of sterile abscess, but with the standardized products of today, alum is probably not the cause of the isolated reactions of this type seen at present. Further discussion of the mechanism of the production of sterile abscess will be presented in the discussion of the following case.

#### CASE REPORT

The patient was a forty-one-year-old white man, single, Coast Guard enlisted, who gave no past history of any allergic symptoms. The past history was negative except for childhood exanthemata. Physical examination at the time of enlistment on September 10, 1942, was completely normal except for a number of missing teeth.

On October 19, 1942, he was given his first tetanus injection. This consisted of 0.5 c.c. of the alum-precipitated toxoid given by deep subcutaneous injection. The next day he reported to the medical office complaining of malaise, feverishness and running nose. His arm was sore. Physical examination revealed signs of a nasopharyngitis. There was no mention made of the patient's temperature or the appearance of his arm at the time. Throughout the next few days he improved subjectively and his temperature was recorded as normal on two occasions. On October 28, 1942, however, his temperature was 101 and he complained of his arm being very sore. The arm was treated with hot wet dressings. The next day his temperature was still 101, and the following day 100. By November 2, 1942, his temperature was normal and he was apparently symptom free.

On November 18, 1942, the patient was vaccinated for smallpox and was given his first typhoid inoculation. His second and third typhoid inoculations were given on November 25, 1942, and December 2, 1942, respectively. There was no unusual reaction to any of these procedures.

## STERILE ABSCESS—RAWSON

On December 17, 1942, the patient was given his second tetanus injection, which consisted of 0.5 c.c. of alum-precipitated toxoid given by deep subcutaneous injection. On December 22, 1942, he was admitted for treatment at the medical office because of a sore arm. He stated that for two days following the injection he had had feverishness, malaise, and vomiting. Examination showed an indurated, red, pointing area measuring 2 cm. by 2 cm. on the lateral aspect of the right arm. This was treated with hot soaks. On the following day the abscess was incised and 10 c.c. of pus evacuated. A drain was inserted. Hot dressings were continued and the drain gradually removed. By January 5, 1943, the lesion was completely healed. No examination of the pus was done.

On November 9, 1943, the patient was given his "booster" tetanus injection which consisted of the same amount of alum-precipitated toxoid administered in a similar manner. On November 15, 1943, the patient returned to the medical office complaining of a painful area on his left arm at the site of the injection. He stated that he had again been feverish, and had vomiting and generalized muscular aches immediately following the injection, and persisting for two days. He was not absent from work, however. Examination revealed an area of redness, tenderness, and induration measuring 3 cm. in diameter over the left deltoid. There was a furuncle at its center, and a large tender node in the left axilla. The patient's temperature was 37.3. He was treated by bed rest, hot soaks, and sulfathiazol, 1 gram q.i.d. The induration had decreased by the next day and treatment was continued another twenty-four hours. The following day some fluctuation was evident and the patient stated that a large amount of yellow pus had escaped spontaneously. On November 18, 1943, the abscess was incised and 15 c.c. of yellow pus evacuated. The wound was packed with iodoform gauze. It continued to drain for several days and by November 28, 1943, was completely healed. A culture of the pus on plain agar showed no growth after one week.

Because of the necessity for finding some way to immunize this individual against tetanus in line with the standard Coast Guard routine, the need became apparent for finding out just which constituents of the toxoid the patient reacted to. Consequently, on December 1, 1943, 0.25 c.c. of 4 per cent alum solution in distilled water (twice the concentration allowed in commercial toxoid) was injected into the deep subcutaneous tissue of the right arm. At the same time 0.5 c.c. of formolized toxoid was injected in the left arm. The following day the patient complained of nausea, vomiting, and malaise. His temperature was 100.8. There was no reaction on the right arm, but the left arm (into which the toxoid had been injected) presented a severe reaction with a zone of tenderness, erythema and edema measuring four inches in diameter. Bed rest was prescribed. The following day the patient's temperature was 100.4. His general symptoms persisted unabated and he then had diarrhea as well. The right arm showed no reaction except minimal point tenderness whereas the left arm showed a slightly greater local reaction than previously with an enlarged tender left axillary node, and a lymphangitic streak extending up the inner side of the left arm. From this point on, the general and local symptoms subsided until by December 8, 1943, all reactions had subsided. Fluctuation was never noted.

### DISCUSSION

Hitherto it was believed that alum was the chief abscess producer in the precipitated toxoid. This was undoubtedly true in former days when large numbers of sterile abscesses were seen following the use of toxoids with a high alum content. The case just described, however, indicated another mechanism in the cases seen today, which are probably cases of individual idiosyncrasy. This patient did not react at all to alum even though the administered concentration was twice the standard. On the



other hand, he was extremely sensitive to the toxoid itself, responding with definitely allergic symptoms, both local and general.

The alum-precipitated toxoid consists of a suspension of precipitated particles, whereas the formolized toxoid is a clear fluid. The difference in the type of reaction to the two preparations is easily explained on purely mechanical principles. The particles of the former hold the allergen in constant contact in considerable concentration with the same small area of tissue, whereas the fluid toxoid easily diffuses over a wide area. Hence the former produces a localized abscess, while the latter gives a diffuse reaction. In either case the offending substance is the same, namely, an allergenic protein substance.

As for the future treatment of the case just presented, it would seem that fluid toxoid would be but a poor substitute for the material used, as the offending agent would still be present and capable of producing a severe reaction, even though of a different type. The possibility of omitting active tetanus immunization in these cases is one which should be considered.

## SUMMARY

1. Reactions to alum-precipitated and formolized toxoids are discussed.
2. A case of recurring sterile abscess complicating alum-precipitated tetanus toxoid is presented.
3. The distinction between the former and the present cause of sterile abscess is made.
4. The problem of prevention of sterile abscess is considered.

## SUMARIO

1. Se han discutido las reacciones al alumbre-precipitado y a los toxoides formolizados.
2. Se ha presentado un caso de un absceso estéril recurrente, complicando el alumbre-precipitado de tétanos toxoído.
3. Se ha hecho la distinción entre la anterior y presente causa del absceso estéril.
4. Se ha considerado el problema de la prevención del absceso estéril.

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## Molar Standardization of Ragweed Pollen Extracts

*(Continued from Page 144)*

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ALLERGIC REACTIONS TO LIVER EXTRACT. Kaufman, R. E., Farmer, Lawrence, and Reich, Carl: *Ann. Int. Med.*, 19:768, (Nov.) 1943.

To the fifty reported cases of sensitivity to liver extract, the authors add eleven more. Their findings are tabulated, and among other things emphasize that the commercial brand of the extract has no relation to the incidence of reactions. In most patients, the reaction occurs rarely after the very first injection, or, if it does not appear initially, comes on when there has been a long interval since the termination of a previous course of injections. There are many more mild reactions than the published reports would indicate, the most common reaction being urticaria. Skin testing is not an absolute criterion since the intradermal test with the extract is difficult to interpret; although the authors feel that a wheal with pseudopods over 15 mm. in diameter is to be taken as a positive reaction when less than 0.05 c.c. of the material is used for skin tests. The authors feel that unit dosage should be the governing factor in the prevention of future reactions in sensitive individuals; and recommend desensitization with subsequent injections. These should be given in small doses and at more frequent intervals; at least once weekly.

L. J. H.



FRENCH K. HANSEL, M.D.  
*Saint Louis, Missouri*  
President, 1944

# Editorial

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## THE ANNUAL MEETING



Elsewhere in this issue is published the preliminary program of the First Annual Meeting of the American College of Allergists, to be held at the Palmer House, Chicago, June 10 and 11, 1944. The American College of Chest Physicians will hold their Tenth Annual Meeting at the Stevens Hotel, Chicago, June 10-12, and the American Medical Association session will be held at the Palmer House, June 12-16.

The scientific exhibits of the AMA will be located on the fourth floor of the Palmer House, and the industrial exhibits at the Stevens Hotel.

Thus, in six days an unusual opportunity is afforded the medical profession to combine intensive instruction with diversion and relaxation.

Seven excellent instructional courses will be given by the College on Saturday and Sunday mornings, June 10 and 11. Saturday morning, from 8:30 to 10:30, Dr. French K. Hansel, Washington University School of Medicine, will conduct the course on Otorhinolaryngologic Allergy; Dr. Jerome Glaser, of Rochester, New York, the course on Pediatric Allergy with Dr. Charles Miller, Corona, Long Island, Commander Marion Sulzberger (MC) USNR, and Dr. Ralph Bowen, Houston, Texas, as collaborators. At the same time Dr. T. Wood Clarke, Utica, New York, and Dr. J. Warrick Thomas, Cleveland Clinic, will conduct a course on Allergy of the Central Nervous System—Doctor Clarke's lecture will be devoted to Cerebral Allergy and that of Doctor Thomas to Ocular Allergy and Allergic Headaches; Dr. Orval Withers, University of Kansas Medical School, will head a course on Gastro-Intestinal Allergy at this time. On Sunday morning, from 8:30 to 10:30, Dr. Louis A. Brunsting, Mayo Clinic, will conduct a course on Dermatologic Allergy; Dr. Leon Unger, Northwestern University Medical School, will lead a course on Asthma, and Dr. Ethan Allan Brown, New England Medical Center, Boston, one on Drug Allergy.

These courses will be practical and devoid of formal discussion, allowing the instructor to present the subject uninterrupted. The leaders are widely experienced teachers in their field so that the registrants should have their knowledge greatly refreshed and be stimulated to do more thorough work when applying allergy to their practice. It is hoped that all the members of the College, as well as candidates and nonmembers, will take advantage of this opportunity and register early. Excellent facilities have been arranged for these courses on the Club Floor of the Palmer House.

The Symposium on Service Allergy, Saturday morning, following the instructional period, will be conducted by the leaders in their respective

fields in allergy in the Military and Public Health Service. War problems in allergy will be featured. The vast amount of material at hand and the use of standard methods make these observations invaluable and unique in the history of allergy.

Colonel Sanford W. French (MC) USA, and Major Lawrence J. Halpin (MC) AUS, Fourth Corps Command, Atlanta, will present statistics covering thousands of cases from their 84 allergy stations when discussing Allergy in the Army. Lt. Col. L. E. Lieder, Army Service Forces, Walter Reed General Hospital, Washington, D. C., will be the commentator.

Commander Marion Sulzberger (MC) USNR, New York, will discuss "Allergic Dermatoses in the U. S. Navy," and will have Lt. Morris Lieder (MC) USNR, Dispensary, U. S. Naval Station, Pensacola, Florida, as commentator.

Dr. Louis Schwartz, Medical Director, U. S. Public Health Service, Bethesda, Maryland, will discuss "Allergic Dermatitis in the War Industries," with Dr. Samuel M. Peck, Senior Surgeon, U. S. Public Health Service, Bethesda, as commentator.

The College is indeed fortunate to obtain such an array of talent for its first annual convention.

Another leading feature of Saturday's program is the Scientific Section, commencing at two o'clock. The Guest of Honor, Dr. Sanford W. Hooker, Professor of Immunology, Boston University Medical School, will be introduced by the President of the College, Dr. French K. Hansel, when Doctor Hooker will open the program with a scientific address. At this session there will be five other 25-minute papers read mainly on the Physiologic, Pathologic and Immunologic Aspects of Allergy. The participants are Dr. Arthur F. Coca, Lederle Laboratories, Pearl River, New York; Dr. Mary H. Loveless, The New York Hospital, New York City; J. Bronfenbrenner, Ph.D., Professor of Bacteriology, Washington University School of Medicine, St. Louis; Dr. Chas. F. Code, Professor of Clinical Physiology, Mayo Foundation Graduate School of the University of Minnesota, Rochester; E. C. Stakman, Ph.D., Chief, Department of Plant Pathology and Botany, Department of Agriculture, University of Minnesota, Saint Paul.

Following the Scientific Session, Saturday evening will be given over to relaxation and social informalities preceded by a cocktail hour of good fellowship. There will be an informal dinner after which President Hansel will make a short address preceding the feature entertainment of the evening. Dr. Herbert Rinkel, Kansas City, will show his famous motion picture with color and sound (symphony music) "Symphony of the Seasons." This unusual classic leaves a pleasant memory with all who have been fortunate to see it.

Sunday morning, following the instructional courses, a series of ten short, practical papers will be read by members of the College, covering a wide field of allergic diseases.

## EDITORIAL

Sunday afternoon will be devoted to a regular business meeting with election of officers, reports of committees, et cetera.

Last but not at all least, an attractive program for the ladies has been arranged under the chairmanship of Mrs. Leon Unger. There will be headquarters for the ladies where they may register and become acquainted, and some enjoyable features are being planned.

Since many of the College members are in the Service and very few on this honor list can be present, all those not in the Service should consider it their duty to unify and promote the specialty of allergy at home by attending this first epochal meeting of the College.

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### OUR GUEST SPEAKER

Dr. Sanford B. Hooker, guest speaker at the first annual meeting of the American College of Allergists, has been attracted to science since his graduation from Dartmouth College in 1909. He received his Ch.B. from Boston University in 1912, and in 1913 received the degree of Doctor of Medicine, *magna cum laude*, after four years of an impressive academic career. Boston University School of Medicine numbers him among its most distinguished alumni.

Upon graduation, Dr. Hooker started advanced studies under Theobald Smith, William H. Park, Ludwig Hektoen, and Frederick P. Gay. In 1916 he received the degree of A.M. from the University of California. Already a research-associate at the Evans Memorial Hospital in Boston, he remained in that position until in 1918, when Base Hospital 44 was mobilized; he was then occupied in various laboratories in France from July, 1918, until October, 1919.

On the boat returning from France, Dr. Hooker turned over in his mind the then novel group-properties of human blood, discovered by Dr. Landsteiner in 1900 but little utilized before the war. It seemed to him that if one injected rabbits with cells of Type II, and absorbed the immune serum with type I, an agglutinin specific for type II might be left, and so on. Before the boat landed, he had it all figured out. It remained only to inject the rabbits and make the tests. It worked out perfectly, except that in the process he discovered an apparent antigenic relationship between the A and B antigens, as we now call them, and discovered, too, another agglutinin which may have been anti-O, or perhaps anti-N, both unknown at that time.

From that time to this, papers have not ceased to issue from Dr. Hooker's laboratory. He became interested in diphtherial and scarlatinal immunization, in streptococci, and in human supersensitiveness. In the course of his work in the latter field, he was led to observe that the very small amount of horse serum, contained in the toxin-antitoxin mixtures used at that time to immunize against diphtheria, was sufficient to render a considerable proportion of the recipients sensitive to horse serum.

A reading of Landsteiner's papers and of H. G. Wells' Chemical As-

pects of Immunity extended Dr. Hooker's interest in the direction of immunochemistry, and since about 1930 he has published a considerable number of fundamental papers on this rapidly expanding and developing subject. Subjects such as the valence of antibody, the mechanism of the precipitin-reaction, the production of more than one quality of antibody by an antigen, and the requirements for antigenicity were discussed. Extending the work of Landsteiner in this field, he showed that antibodies to a drug such as strychnine could be produced, if the drug were properly-coupled chemically to a protein-carrier and injected. In connection with the mechanism of serological reactions, a controversy, characteristic in its urbanity and dialectic skill, developed between Hooker and his followers and the "lattice" school of Marrick and of Heidelberger. While the main point at issue does not seem yet to have been settled, the discussion has undoubtedly been largely responsible for the contribution of much knowledge, and indirectly for drawing new workers (as for example the chemist Pauling) into the field.

Dr. Hooker was president of the Society for the Study of Asthma and Allied Conditions in 1935-36 and of the American Association of Immunologists in 1936-37. He is an editor of the *Journal of Immunology*, for several years was on the editorial board of the *Proceedings of the Society for Experimental Biology and Medicine*, and edited the section on immunology in the *Yearbook of Pathology and Immunology*, which appeared in 1940 and 1941.

Characteristics of Dr. Hooker have always been the rigor of his thinking and the keenness of his observation. It would be hard indeed to find one of his papers in which the conclusion did not follow logically from the evidence available. His observational skill is remarkable. In the course of an experiment designed as a routine check of a predicted effect (which effect generally comes off), he has been known again and again to notice some new fact which marks a totally new contribution to knowledge.

From instructor he was promoted to Assistant Professor of Immunology at Boston University School of Medicine in 1921, Associate Professor in 1924, Professor in 1932. He has been immunologist to the Massachusetts Memorial Hospital for many years, and a member of the Evans Memorial since about 1920. As a teacher at B.U.S.M. since 1913, Dr. Hooker is probably remembered (affectionately) by the few rather than the many. This is undoubtedly as he would wish it. To students whose eyes are set solely on a medical degree and a lucrative practice, Dr. Hooker's lectures may indeed at times have seemed positively maddening with their requirement of close attention to detail and rigorous thinking. But to the real student, interested in gaining an insight into a difficult subject and in acquiring the ability to make his own contribution, Dr. Hooker's lectures have been a delight, both for their conciseness and clarity. When given suitable student material, Dr. Hooker has shown to a rare degree the gift of teaching and inspiring, even though his own interests are

primarily in investigation. Men such as he comprise the most important contribution of our Universities to the scientific life of our times.

W. C. BOYD

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## VETERINARY ALLERGY

Preceding the regular session of the College at Chicago next June 10 and 11, there will be a joint informal meeting of the veterinarians representing the American Veterinary Medical Association and the members of the American College of Allergists at the Palmer House, Friday afternoon, June 9.

The *purpose* of the meeting is to organize a section of the College known as the Veterinary Section of Immunology and Allergy. The *plan* is to closely coördinate the investigative and clinical observations of immunology and allergy observed in the lower animals with those in humans in a united effort to further our knowledge of these subjects for the health betterment of both man and animal.

It is proposed that those members of the American Veterinary Medical Association who have contributed and are interested become Associate Fellows in the College; and that a regular section composed of this group of scientists and those in the College with allied interests meet annually.

At these sessions scientific papers embracing all phases of the subject, as well as round table and panel discussions, will be presented. The Executive Committee would be comprised of equal representation from both interested groups who would conduct the business affairs of the section. It is also proposed that a fund be established for stimulating research in immunology and allergy of animals. Funds and trained men are essential.

For the first meeting, a tentative program has been arranged with the informal sanction of the officials of both societies which is published in this issue. The program will be presented on the fourth floor of the Palmer House where the regular session is to be held. There has been an enthusiastic response to present papers at this first meeting of such a nature ever held which promises to be very largely attended. Dr. J. G. Hardenbergh, Secretary, American Veterinary Medical Association, headquarters in Chicago, endorses the plan.

Although chemist Pasteur, over sixty years ago, proved the value of teamwork in the various sciences, progress has been retarded by isolationism. Today, experimental anaphylaxis, clinical allergy and immunity to infection are considered by the majority of all investigators as basically the same, and each is the result of a similar underlying mechanism, whose manifestations of reaction are determined by secondary factors.

With the accumulating and increasing knowledge of immunology and allergy made available by the present war, a way should be made for a united effort of scientists for a peacetime program. All those interested are invited to attend. A tentative program appears on page 135 of this issue.

F.W.W.



# Progress in Allergy

Under the direction of ETHAN ALLAN BROWN

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## The Vitamins and Allergy

ETHAN ALLAN BROWN, M.R.C.S. (LONDON), L.R.C.P. (ENGLAND), F.A.C.A.

The scientific literature which concerns itself with the vitamins can be divided into several categories. There is at first the work on the purification of those vitamins already known and their application to known vitamin deficiency conditions. There is the discovery of new vitamin fractions inherent in which is the possibility that there are previously unsuspected avitaminoses. There is the work on the effect on normal physiological processes of the presence or absence of adequate vitamin intake. Lastly as each vitamin becomes widely available and relatively inexpensive in cost, the attempt to treat diseases or conditions not known as avitaminoses and not associated with typically physiological abnormalities. An examination of the Cumulative Index for the last 15 years shows that there are few if any of the ills to which human flesh is heir to which, with no scientific basis, have not been treated with any one or all of the known vitamins.

As far as an internist interested in allergic problems is concerned the following problems must be answered. First, is sensitivity (using the word in its broadest meaning) due to any vitamin deficiency? Second, if it is not mediated by a vitamin deficiency can accessory food factors given in abundance affect the clinical course of any allergic disease? Third, can any vitamins have any effect upon any of the conditions not due to but associated with allergy although they are not direct causative factors.

It must be said at the moment that we have no clear indication that allergy in human beings can in any case be caused by a vitamin deficiency. It is possible, however, that such deficiency although not primarily important has a secondary effect. This can only be proved, unscientifically to be sure, and in the most haphazard way by watching the effect upon patients of the ingestion of large amounts of the more easily available preparations. Unfortunately many of the papers recording the effect of such work are not worth listing for the simple fact that the original conditions are not so well described; that the diagnoses are without question. Usually there are no adequate controls; the improvement reported upon is subjective in type; the vitamins are occasionally given in numbers so that the improvement if any cannot be pinned upon any special one. Many investigators did not know or lost sight of the fact that vitamin A is concerned with the metabolism of epithelial tissues arising from ectoderm and endoderm, that some of the vitamin B fractions affect ectodermal structures and vitamins C and D with mesodermal tissues and that a number of secondary factors including the presence or absence of infection, the ingestion of alcohol, the mineral intake, and the endocrine balance all may vary the response to vitamin ingestion.

Frei<sup>14</sup> has shown that in guinea pigs vitamin A has no significant influence upon sensitization by old arsphenamine. Groups of guinea pigs first sensitized and then tested to old arsphenamine and later placed upon very high or very low vitamin A diets reacted to the intracutaneous injections of old arsphenamine in an identical way and to the same degree as they did before their diets were changed. Other animal experimentation, however, has shown that there may be relationship between vitamin A and the sympathetic nervous system. Thiele and Guzinski<sup>47</sup> demonstrated that after epinephrine injections the liver became almost entirely vitamin

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A free, the injection of epinephrine elevating the vitamin A level of the blood. Another possible secondary relationship between vitamin A and allergic conditions is suggested by the work of di Sant'Agnese and Larkin<sup>7</sup> who found that in four cases of intractable infantile eczema each was characterized by retarded development, malnutrition, marked lymphadenopathy, high blood eosinophilia, frequent severe respiratory infections and a severe generalized eczema refractory to local or dietetic treatment. An examination of the vitamin A blood levels before and after the ingestion of oleum percomorphum demonstrated that the patients had a vitamin A deficiency supposedly resulting from a defect in intestinal absorption, the authors feeling that the respiratory infection and the malnutrition were due to this fact.

In work including other vitamins with vitamin A it was shown by Kuttner<sup>27</sup> that large doses of vitamins A, B, C, and D had no effect upon the number of upper respiratory infections of a group of 108 rheumatic children. The weight gains of this group and the control group were essentially the same as was the response to infection. In addition a symposium arranged in 1939 under the auspices of the Council on Pharmacy and Chemistry and the Council on Foods of the American Medical Association also concluded that it had not been proven that the administration of vitamin A over and above the normal requirements conferred any exceptional immunity to respiratory disease.

The situation as far as vitamin B complex is concerned is more difficult to evaluate. The vitamin B complex includes such differing factors as thiamine, riboflavin, nicotinic acid (niacin), pyridoxin choline, biotin, panthothenic acid, Maturation factor, Gray hair preventive factor, Liver damage preventive factor, Curative factor for egg white injury and a number of other factors including factor W and factor U. The present picture of vitamin B deficiency in no way suggests any clinical syndrome typical of allergy, in human beings.

In animals Kim and Lee<sup>24</sup> reported that anaphylactic shock in guinea pigs could be inhibited, if vitamin B was given during the sensitization period or one hour prior to the administration of the shocking dose. Wedgewood and Grant<sup>54</sup> stated that rats could only be allergized when on a vitamin B deficient diet.

From the medical point of view vitamin B<sub>1</sub> has been used with varying success. Morehead<sup>25</sup> reported upon a case of chronic bronchitis and severe asthma for which immediate relief was secured with 30 mg. thiamine given intravenously with complete recovery of both conditions following six months of treatment with 3000 mg. thiamine-HCl given intravenously in doses of 30 to 40 mg. at intervals of six to eight hours at first, and later once daily the injections being supplemented with oral administration of the vitamin B complex. He also reports seven other patients similarly treated with satisfactory results. It has been stated by Shannon<sup>42</sup> that thiamine hydrochloride taken orally or by injection will protect patients from mosquito bites relieving the itching and eliminating formation of a papule. A dosage of 40 mg. given every four hours brought relief within twenty-four hours to ten patients who thereafter took maintenance doses as necessary. The effect of thiamine chloride on itching conditions of the skin had previously been reported upon by the same author who stated that large doses of thiamine taken orally controlled the itching associated with a number of conditions including morbilli, urticaria, eczema, scabies, pityriasis rosea, and other conditions, the doses varying from 20 to 40 mg. a day. The itching of the skin in all but six of thirty-five patients was controlled by these means.

Thiamine on the other hand has been reported as causing sensitivity. Schiff<sup>40</sup> in the *Journal of the American Medical Association*, described a patient who had been given several courses of intramuscular injections of thiamine for the treatment of arthritis. Given a routine dose the patient collapsed, her pulse becoming imperceptible, respiration ceasing within one minute following the injection. Arti-

ficial respiration was instituted and epinephrine 1 c.c. was given intravenously. The patient recovered. Scratch tests with aqueous and commercial solutions of thiamine hydrochloride showed positive skin-test reactions. The remaining ingredients of the solutions gave negative reactions. Passive transfer tests were negative. The shock reaction was said to have been due to an acquired sensitivity to thiamine hydrochloride.

Other cases of thiamine chloride hypersensitivity have been described. Among others one by Laws<sup>28</sup> and two by Eisenstadt.<sup>11</sup> The first a white woman aged seventy-two, received subcutaneous injections, thirty for ten days and then weekly for eight weeks and thereafter at ten-day intervals. Within thirty minutes after her last injection she developed generalized urticaria, angioneurotic edema with dyspnea, wheezing and cyanosis. Responding within a few hours to an injection of epinephrine the patient gave positive skin tests and positive passive transfer tests to the aqueous and commercial preparations of thiamine hydrochloride, a time interval of ten days having elapsed between the previous injection and the one which caused her reaction.

The patients described by Eisenstadt<sup>11</sup> responded, the first, with angioneurotic edema, and the second, with local swelling and itching. Both patients, however, were able to tolerate thiamine by mouth. Both gave positive skin test reactions but negative passive transfer tests.

Carlström<sup>8</sup> and his colleagues pointed out why some cases of vitamin B<sub>1</sub> deficiency failed to respond to its administration. They suggest that flooding the system with thiamine results in the binding of large amounts of pyrophosphate probably excreted in the urine. The treatment would then remain without effect until this loss of pyrophosphate was replaced since the vitamin B<sub>1</sub> combines in the body with the pyrophosphate to form an enzyme needed for the oxidation of pyroracemic acid. They report on seven patients who did not respond to vitamin B<sub>1</sub> until they were also given the pyrophosphate.

The vitamin B complex containing all the factors has been reported as affecting the course of infantile eczema. Kristensen<sup>26</sup> found vitamin B<sub>1</sub> to be ineffective but he and Vendel<sup>50</sup> stated the complex was "infallible" in the treatment of acute or chronic eczema. In this country, Harris and Gay<sup>17</sup> stated that of twenty infants, two given the vitamin B complex healed completely, eleven improved and seven showed no change.

Although migraine is not usually allergic in origin, a sufficient number of the patients desiring study for the discovery of allergenic causes remain to be treated by allergists. Of interest is a paper by Palmer<sup>37</sup> who treated forty-eight cases of migraine with vitamin B<sub>1</sub> intramuscularly supplemented by oral doses of the vitamin B complex. Twenty-three of the patients were completely relieved, some remaining free from recurrences as long as seven months after therapy had been terminated. Although 58.8 per cent of these patients reported relief from ergotamine tartrate, 70 per cent were relieved by thiamine hydrochloride. In a later series the same author stated that 75 per cent or twenty-four out of thirty-two attacks of severe migraine were interrupted within two to three hours after an intramuscular injection of 30 to 90 mg. of thiamine hydrochloride.

If it is believed that some of the patients demonstrating a typical Ménière's syndrome may be allergic. It is interesting to note that Harris and Moore<sup>18</sup> gave thiamine chloride to twenty cases, supplementing it with nicotinic acid, seventeen of the patients becoming entirely free from vertigo and the other three presenting a marked improvement following two to three months of treatment. The dose was vitamin B<sub>1</sub>, 20 mg. daily and nicotinic acid, 250 mg. daily.

Kalber<sup>22</sup> reported that in three patients with chronic bronchial asthma the subcutaneous administration of 1 mg. of vitamin B<sub>2</sub> (Lactoflavin) combined with 1 mg. of adenosin phosphoric acid given at intervals of from five to eight days caused great improvement. In some patients, however, there was no change.

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In 1938, Madison, Fish and Frick<sup>29</sup> reported that nicotinic acid in massive doses augmented the production of specific precipitin antibody while small doses caused a diminution in antibody production. The effect noted was not as great as that produced by ascorbic acid.

It was shown in animal experimentation by Soldati<sup>43</sup> that dogs deprived of the complete vitamin B complex resisted both the bradycardiant action of injection of pitressin as well as the tachycardiant action of atropine. They reacted normally, however, to injections of acetylcholine. Of interest to the allergists, however, is that their vascular systems responded to epinephrine with a hypertensive reaction more intense than those exhibited by dogs on normal vitamin B complex containing diets.

During the same week in May, 1943, Suranyi<sup>46</sup> in Switzerland and Melton<sup>34</sup> in England published papers on the treatment of allergic conditions with nicotinic acid. Suranyi noted that the oral administration of nicotinic acid produced symptoms similar to those following the injection of histamine and therefore used the substance experimentally for patients suffering from bronchial asthma and urticaria. The dose was 0.025 to 0.05 Gm. twice daily before meals for three weeks for those patients in whom nicotinic acid orally produced an erythema. Melton gave 50 to 100 mg. of nicotinic acid intravenously to nineteen patients during one or more acute paroxysms of bronchial asthma achieving definite improvement in sixteen but marked exacerbations in two. In thirty patients who were having frequent and severe paroxysms which were not easily controlled by ephedrine, nicotinic acid was given between attacks in a 50 mg. dose two to three times daily. In sixteen of these patients the severity and frequency of the attacks were definitely reduced, relapse occurring when the ingestion of the drug was discontinued. Twelve patients given control injections of sterile water in order to make certain there was no psychological factor did not show the same response. For the patients receiving the material by mouth, control tablets of citric acid were given in which cases there were frequent relapses.

Maisel and Somkin<sup>31</sup> gave twenty-nine intravenous injections of .1 Gm. of nicotinic acid to twenty-one patients who were suffering severe asthmatic attacks or were in status asthmaticus. Nine patients were given 0.2 Gm. of nicotinic acid orally three times daily before meals. Their relief appeared to coincide with the appearance of a flush. None showed untoward reactions or acquired tolerance during the period they were observed. The authors felt that nicotinic acid diminished both the frequency and severity of asthmatic attacks in about 70 per cent of their patients.

Murano<sup>36</sup> also gave nicotinamide therapy to infants suffering from eczema. He stated that there was rapid relief from the itching and disappearance of the other skin symptoms in two to three weeks. For the first seven to ten days he gave ten centigrams intramuscularly the injection being given every other day for ten days more. Oral therapy of two to three tablets containing twenty centigrams each was given on the days on which the patient took no injection. Some of the patients manifested flushing and restlessness.

In 1939 McGinty<sup>33</sup> and in 1940 Doughty<sup>8</sup> reported on the effect of nicotinic acid upon patients receiving large doses of sulfanilamide. The first stated that the mental apathy so often present with the ingestion of sulfanilamide and that the other depressive symptoms and the porphyrinuria were decreased. Doughty reported on complete relief of headache and nausea when nicotinic acid was administered so that the administration of sulfanilamide could be continued more easily.

There are a few positive reports as to the effects of vitamin B<sub>6</sub> upon any allergic condition. Of interest, however, is a paper by Vilter, Aring and Spies<sup>51</sup> on a case of peripheral neuritis due to arsenic which could be brought into partial remission by intramuscular injections, at first, of pyridoxin alone and more spectacularly when

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the patient received vitamin B<sub>6</sub> 20 mg. and alpha-tocopherol 50 mg. intramuscularly twice daily. The patient relapsed when saline or thiamine were administered instead, or when the vitamin B<sub>6</sub> was discontinued. To maintain improvement, however, the vitamins had to be administered daily.

Despite the discouraging reports, work in progress with some of the other fractions of vitamin B complex suggest that they may play a part in allergic conditions. These will be reported upon in the near future.

Since it would be obviously impossible to review all of the literature concerning the relationship between vitamin C and those conditions which, in any sense of the word, may be allergic, an arbitrary limit was set and only the work done during the last five years was studied.

The evidence that vitamin C deficiency is a cause of allergization is by no means conclusive. In 1935 Sulzberger and Oser<sup>45</sup> reported that guinea pigs deficient in vitamin C could be sensitized to arsphenamine more readily than those which were taking normal amounts. In the following year Steinback and Klein<sup>44</sup> reported that animals had an increased tolerance to tuberculin when given sufficient vitamin C. In the following two or three years it was reported by Cohen<sup>4</sup> and also by McDonald and Johnson<sup>32</sup> that the presence or absence of vitamin C had no effect either upon an animal's capacity for becoming sensitized eczematogenously to arsphenamine or to poison ivy or, upon its tendency to go into anaphylactic shock. Kile and Pepple,<sup>23</sup> on the other hand, reported that animals showing marked signs of vitamin C deficiency could not be sensitized. In 1939, Yoshikawa<sup>56</sup> reported that the guinea pigs were more easily sensitized if given small quantities of vitamin C but incapable of being sensitized when given large amounts; moderate intake having no effect.

For human beings Walzer,<sup>53</sup> reviewing the literature, felt that the definite role for vitamin C in experimental human hypersensitivity had not yet been established and Bundeson<sup>2</sup> and his colleagues, reporting in the *Journal of the American Medical Association* in 1941, felt that there was no clear evidence that human allergy could be affected by vitamin C intake.

Dragstedt,<sup>9</sup> in 1938, set out to study the relationship between vitamin C and peptone shock in dogs. Previous workers have stated that the administration of vitamin C inhibited anaphylaxis in sensitized guinea pigs but did not protect them against histamine shock, assuming that the vitamin C prevented the liberation of histamine but could not inhibit its action after it had been liberated. Dragstedt and his colleagues discovered that the administration of vitamin C prior to the induction of peptone shock in dogs failed to prevent their reactions. He and his colleagues concluded that vitamin C does not prevent anaphylaxis by inhibiting the liberation of histamine. In the next year, however, Yokoyama<sup>55</sup> reported that he could prevent anaphylactic shock in sensitized guinea pigs by injecting ascorbic acid immediately before a second injection of horse serum. The reaction was also prevented if the horse serum was mixed with ascorbic acid before injection. The Schultz-Dale reaction of isolated intestine from sensitized guinea pigs was inhibited if ascorbic acid was added to the Ringer-Locke solution five minutes before adding the horse serum. A slight reaction was obtained under the same circumstances in isolated uterine strips but the author explained the slight reaction by considering the uterine muscle more sensitive than the intestinal.

Studying the effects of vitamin C upon specific precipitin production against the injection of bacterial vaccines in rabbits Madison, Fish and Frick<sup>30</sup> concluded that there was an increase in the precipitin production but a marked decrease in the specific agglutinins. They postulated two competitive defense mechanisms responsible for humoral immunity. One of these might be an extracellular synthesizing process and the other an intracellular lytic process. If this were true, vitamin C activation of tissue enzymes might increase the precipitin production and yet reduce the yield of specific agglutinins. It would mean that vitamin C, valuable to

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the treatment of infections, would have little or no value when used as an adjuvant to vaccine therapy.

The following year Walther<sup>52</sup> using rabbits and also guinea pigs shocked them by the intratracheal introduction of the specific antigen of the pneumococcus. His histological study of the animals showed the presence of marked hemorrhage, emphysema and widespread distribution of eosinophilia in the alveoli, the bronchi and the interstitial tissues. The pretreatment for seven days with large amounts of vitamin C previous to the shocking injection did not decrease the local anaphylactic pulmonary response and in some cases seemed to intensify it. In the same year Ardy<sup>1</sup> reported that guinea pigs kept on either a high vitamin C or a low vitamin C diet showed no variation in their blood complement. In the following year Ecker<sup>10</sup> reported a definite correlation as existing between the ascorbic acid content and the complementary power of the blood serum of guinea pigs. He found that the complement which had been inactivated by iodine, hydrogen peroxide, quinine and iodoacetate could be reactivated with various reducing agents as ascorbic acid, hydrogen sulphide and potassium cyanide. Complement taken, however, from anaphylactic animals could not be reactivated in the same way.

Freidman<sup>15</sup> studied the contractile response of the isolated smooth muscle of the guinea pig to stimulation with histamine under conditions of vitamin C deficiency and adequate diet. In the isolated smooth muscle preparations of the animals suffering from scurvy the minimal stimulating dose of histamine was at least one thousand times as great as that in the control group, the diminution in contractile response developing after the animals had been on the scorbutogenic diet for three or four days, remaining constant up to thirty-five days.

Ruskin<sup>39</sup> devised an ingenious experiment by which the direct effects of drugs could be studied by microscopic examinations of the rabbits' bronchioles. Histamine was applied to produce broncho-constriction and then drugs antagonistic to histamine applied to the constricted bronchioles. After relaxation of the bronchioles by the drugs antagonistic to histamine a second addition of histamine caused a little secondary contraction. Ascorbic acid and sodium ascorbate when used in this manner relaxed the bronchioles but inhibited the constricting effect of the second addition of histamine. When ascorbic acid was added as an acid radical to calcium, ephedrine, benzedrine and epinephrine the ascorbate counteracted the histamine effect although the original compounds which did not contain the ascorbic acid radical promoted histamine activity. Ruskin reported epinephrine ascorbate as antagonizing histamine more quickly and more actively than epinephrine hydrochloride, having twice its bronchodilation capacity. He felt also that there was a relationship between the physiological activity of calcium and histamine and that in the presence of a vitamin C deficiency calcium might definitely be contraindicated in histamine shock.

In a similar experiment Farmer and Kassman<sup>12</sup> dealing with serum-sensitized guinea pigs kept on an ascorbic acid-deficient diet for six to nine days stated that there was no increase of anaphylactic response. Normal guinea pigs kept on an ascorbic acid-deficient diet for the same length of time showed a slight increase in histamine sensitivity. An examination of the ascorbic acid content of the adrenals of the normal guinea pigs kept on an ascorbic acid-deficient diet for seven days showed only a moderate decrease in the amount of ascorbic acid present. The authors felt that the anaphylactic response in the histamine sensitivity depended upon the degree of ascorbic acid depletion of the adrenal glands.

It was not long after the work mentioned above was published that vitamin C was given to human beings suffering from allergic complaints. Studies by Goldsmith, Ogaard and Gowe<sup>16</sup> on thirty-two allergic patients showed that twenty-nine had subnormal levels of ascorbic acid and only three had adequate vitamin C nutrition whereas forty-three control patients presented normal blood vitamin C

levels. Seven patients with bronchial asthma, one with hay fever and one with urticaria were given standardized diets in order to determine whether or not allergic patients required more vitamin C than did normal control individuals. The authors concluded that six of the seven patients with asthma were unable to maintain as high a level of blood ascorbic acid as could a control group under the same regime. In two of the patients the frequency and severity of asthmatic attacks were reduced but, in the other five, the condition was unaffected following saturation of the body with ascorbic acid. These results were not surprising since Hunt<sup>20</sup> had shown three years previously that doses of 100 mg. daily of ascorbic acid had had no effect whatsoever in a group of patients with bronchial asthma.

In five out of seven cases with previous arsphenamine dermatitis Cormia<sup>5</sup> showed that massive intravenous doses of vitamin C with high oral maintenance doses enabled the patients to tolerate the drug. Attempts, however, to sensitize those patients who showed low vitamin C levels, by the intradermal injection of neoarsphenamine failed in every case. Cormia concluded that vitamin C was probably related to arsphenamine sensitization but postulated an X factor necessary for the production of cutaneous sensitivity. This work was corroborated by Delp and Weber<sup>6</sup> in their study of vitamin C levels in one hundred and six patients with untreated syphilis showing that these were in direct proportion to the dietary intake of the vitamin. Groups of patients who had been given treatment with the heavy metals showed no change in the vitamin C values. The authors favored the treatment of arsenical dermatitis with cevitic acid suggesting that such therapy would warrant further study. Vail<sup>49</sup> on the other hand reported that arsenical sensitivity was most commonly associated with a vitamin C deficiency although in a small percentage of cases reactions could occur although the blood vitamin C values were normal. He felt that the best results were obtained by intravenous therapy although oral administration of vitamin C was effective, the symptoms of arsenical sensitivity disappearing as the blood vitamin C increased, the best results occurring in those patients who took small doses of vitamin C at the same time they had their arsenical medication.

Large amounts of vitamin C were soon given to patients with hay fever. Holmes<sup>19</sup> in five patients gave 100 mg. daily for one week in twelve patients 200 mg. doses and in some patients 5 mg. daily, reporting almost complete relief after two to four doses of 500 mg. in all but three patients who completed the treatment. One patient with bronchial asthma was greatly relieved following 500 mg. doses daily for two weeks and a female patient almost completely cured of eczema after 150 mg. daily for one month. One patient responded with a toxic reaction, presenting a rash. Korbsch<sup>25</sup> had reported, five years previously, that doses of ascorbic acid up to 1 gram daily by mouth relieved a number of patients suffering from allergic coryza, serum rashes and erythema multiforme.

More recently Perner<sup>38</sup> prevented the toxic reaction from which a patient had suffered following the use of sulfathiazole by giving him 100 mg. of ascorbic acid with each dose of sulfadiazine. He treated in all, fifty-one patients none of whom showed the usual depression seen after sulfonamide therapy when they were given vitamin C at the same time.

Considering the extent of our knowledge regarding the inter-relationship of calcium and vitamin C it is indeed, surprising that none of the authors listed above excepting Ruskin mentioned this fact although there are many reasons for believing that such an inter-relationship exists. Work in progress and timed for publication in the near future and in the present review will attempt to correlate some of the relationships between the vitamins and minerals in normal metabolism. The inclusion of such work at this time

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would make the present paper too unwieldy for everyday reference and use.

The present paper represents only a brief résumé of some of the contemporary work on vitamin deficiencies and allergy. When it is seen that there have been over ten thousand papers written on the forty or more known accessory food factors it can be understood how impossible it must be to treat the subject adequately. In the limited space at our disposal only an arbitrary period of time (five years) could be reviewed and only the more important papers in the field given study. Future papers in this series will attempt to fill in some of the more obvious lacunæ.

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### ALLERGIC REACTION TO DRIED HUMAN PLASMA. Colonnell, William J., Lt. Commander, MC, USNR: *U. S. Naval M. Bulletin*, 11:1356, (Sept.) 1943.

The patient, who had had two whole blood transfusions from one donor, had urticaria following the second transfusion. The recipient had no personal nor familial history of allergy. The donor was sensitive to ragweed pollen. Following the transfusion, the recipient showed a 3-plus reaction to ragweed pollen, and also a 1-plus to the same activated plasma (Dilution 1:10) used in transfusion. The presence of ragweed allergen in pooled human plasma was demonstrated in passive transfer on three control patients. The third transfusion gave the recipient: angioneurotic edema; asthma and urticaria.

L. J. H.

### MILK INTOLERANCE, THE CAUSE OF A NUTRITIONAL ENTITY. A Clinical Study. McClendon, P. A., and Jaeger D.S.: *Southern M. J.*, 36: 571, (Aug.) 1943.

The authors base their observations upon sixty-five private patients seen during the last five years. In order of frequency, the milk intolerance showed itself by complaints of: constipation, anorexia, abdominal pain, abdominal distress, a sense of fullness, pallor, fatigue, irritability, recurring diarrhea, repeated colds, asthmatic bronchitis, enuresis, and urinary frequency. The degree of intolerance was variable. The patients' histories showed a familial allergy, and excessive ingestion of milk by their mothers during the period of gestation. Each patient followed an identical pattern in each instance. The physical examination showed the patients to have the characteristics of poor nutrition. Case Reports.

L. J. H.

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### Allergy in Otolaryngology and Ophthalmology

#### A Review of the Recent Current Literature

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A review of the literature on the subject of allergy in relation to otolaryngology for the year 1943 shows distinct advances in this special field. Progress, however, seems very slow for there should be many more papers than those presented. There is certainly a great deal of need for further investigation in this field and there should be close coöperation with the allergist. During the past twenty years attention has been called repeatedly to the importance of allergy in its relation to nasal and sinus diseases and yet many otolaryngologists pay little attention to it. Far too many patients with nasal allergy are treated for frequent colds and sinusitis and too many tonsillectomies are performed on children who have unrecognized respiratory allergy. Few ever take the trouble to make a cytologic examination of the nasal secretion. It is true that many otolaryngologists are too busy to spend additional time on allergy patients. Most of them do not have an adequate working knowledge of the subject. Nevertheless, it is the duty of every otolaryngologist to make some provision for the treatment of these patients. Similar conditions exist in the field of pediatrics, particularly in the management of respiratory allergy.

Although this situation appears discouraging, there is now a greater movement on the part of the national allergy organizations to promote the knowledge of allergy in other fields and to bring together all allergists and specialists in an effort to produce closer coöperation.

#### PHYSIOLOGY AND PATHOLOGY

Fowler<sup>12</sup> reports an interesting case of a woman thirty-four years of age who developed a typical Horner syndrome on the left side following removal of the left stellate ganglion for the relief of pain in the left arm. Obstruction and profuse watery discharge appeared on the left side of the nose. Smears of the nasal secretion from this side showed eosinophiles. Skin tests were negative. The symptoms were controlled with syntropan. Among four other patients with Horner's syndrome, one had symptoms similar to the above patient. It was not stated whether eosinophiles were demonstrated in the nasal mucus in this case.

Mohun<sup>26</sup> reported a group of eight cases in which nasal blocking or congestion developed during pregnancy in women who had never had such symptoms when not pregnant. Five of these women had had similar symptoms during one or more previous pregnancies. The symptoms disappeared within one to seven days after delivery.

In another group of twelve women who already had hay fever or nasal allergy, the symptoms were markedly increased during pregnancy. Mohun concludes that the increase in estrogen during pregnancy is probably the etiologic factor.

Unilateral polypoidosis not infrequently occurs in older children and adolescents. dos Reis and Corrêa<sup>8</sup> report their observations on a group of seven cases. The patients varied in age from twelve to twenty-one years, most of them being in adolescence. The Caldwell-Luc operation was successfully performed on all of them. This type of polyp is usually presented in the choana, the attachment being most frequently in the antrum. It is important to differentiate this type of polyp from that of allergic origin. The choanal polyp is not the result of allergy; therefore, it should not be erroneously treated as such.

A most outstanding contribution has been made by Hilding<sup>16</sup> on the relation of ciliary insufficiency to death from asthma and other respiratory diseases. He points

out that there is a group of cases among patients who die from asthma who show a very striking and characteristic change in the bronchial epithelium. The change consists of a substitution of goblet like cells for the normal columnar ciliated cells. Apparently it is a true metamorphosis. As this change takes place, the ciliary mechanism is lost and the characteristic viscid, mucinous secretion accumulates in the air passages. Normally this viscid secretion is very readily carried up vertical surfaces by ciliary action. The amount of secretion is enhanced because the erstwhile ciliary cells are secreting as well as the glands. The difficulty of removal of the secretion is aggravated because the mucin remains attached over large areas within the cells which produce it, thus anchoring the mass to the wall. When the air passages have become completely filled, the patient dies of asphyxia. In Hilding's opinion, this metamorphosis is the chief pathologic change and death results directly from the loss of ciliary function.

He noted a second group of asthmatics in which the cilia were also lost, but the picture was essentially different. This group was characterized by chronic bronchitis with purulent secretion. There was destruction in the surface of the bronchial epithelium and the ciliated cells had sloughed off very extensively. In these patients also the air passages filled up with secretion to such an extent that the patients died. Attention is also called to the fact that bronchospasm was doubtless a factor in some of these cases. In one of the group which was omitted from this discussion, spasm seemed to play a dominant rôle. A patient with tracheobronchitis who died in extreme respiratory distress showed the ciliated epithelium was practically entirely destroyed and all the bronchi contained viscid plugs of secretion. Further studies were conducted on pathologic material from the pandemic of influenza in 1918. The material was not entirely satisfactory, but as far as could be determined the bronchiolar epithelium had been entirely destroyed and all the cilia with it.

In all of these groups, Hilding feels that the mechanical removal of the secretion as a substitute for ciliary action is indicated. Aspiration, either through a bronchoscope or a tracheotomy, would be the best.

In a series of animal experiments, Hilding<sup>17</sup> has shown that certain pathologic conditions in the upper and lower respiratory tracts, such as postoperative pulmonary atelectasis, vacuum headache and retraction of the ear drum, are the result of insufficiency of ciliary activity.

The steps in the development of postoperative pulmonary atelectasis were outlined as follows:

"(1) An excess of secretion is formed within the affected lobe. (2) A succession of occluding masses, or pistons, of mucus form across the lumina of the air passages. (3) These 'pistons' move up the cylindrical air passages by ciliary action, each carrying a quantity of air. (4) As soon as the pressure within the lobe begins to fall, it shrinks by its own elasticity and from pressure by adjacent lobes. (5) The adjacent lobes carried by the force of inspired air move into the space relinquished by the affected one. (6) The advancing pistons rupture serially as they reach tubes of greater diameter and meet more forceful changes of air pressure. Each then releases the bubble of air which is carried and continues on its course as a mural mass of film. (7) A negative pressure of considerable proportion is produced within the lobe when the supply of air is exhausted. (8) The masses of secretion then present in the air passages come to a standstill when the cilia can no longer advance them against atmospheric pressure. (9) The cilia continue to remove secretion from these stalled masses in thin films and might eventually remove them entirely if they were not replaced by continued secretion."

In the experiments regarding vacuum headache, he noted that negative pressure can be produced within a normal sinus by the introduction of a quantity of mucus which replaces a portion of the contained air. When the ostium becomes occluded negative pressure develops within the sinus. The pressure falls as the mucus passes through the ostium. The pressure ceases to fall when it becomes equalized on the

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inside and the outside. The cilia continue to act and remove the mucus in thin films. When sufficient mucus has been removed, atmospheric pressure forces air into the sinus again. In this manner, Hilding states, negative pressure almost certainly develops clinically in sinuses more or less filled with mucus.

The negative pressure which is known to occur in the middle ear is probably caused by the force of ciliary action moving mucus down the eustachian tube.

### DUSTS AND MOLDS

In a group of 100 selected patients, Davidson<sup>5</sup> noted that of ninety-five reacting to house dust, ninety also reacted to animal hairs. In this group he felt that animal hairs were responsible for the production of symptoms in only 10 per cent. This brought up the question as to whether the animal hairs contacted in other ways than from live animals were responsible for the activity of house dusts. On the basis of clinical observation and skin tests, Davidson concludes that the final proof of the constitution of house dust awaits the development of tests by which to differentiate the almost endless number of allergens in it. Some investigators have presupposed the presence of some unknown ingredients in house dust which would account for its activity. He finally concludes that house dust is composed principally of cotton, flax, jute, wool, silk, six or more animal hairs, three or more feathers, glue, kapok, orris root, pyrethrum and tobacco.

Durham<sup>9</sup> has presented a very comprehensive treatise of the subject of air-borne fungus spores as allergens. His report is based upon extensive observations made in the United States, Alaska and some foreign countries. A comparative study of the total seasonal fall of alternaria and hormodendrum spores and ragweed was made in fifty-three cities. In number and in widespread geographic distribution, the spores of stem rust, alternaria and hormodendrum are outstanding. The daily fluctuations of mold spore concentrations are more pronounced than those of pollen and are not as easily accounted for by weather conditions as are fluctuations in the pollen curve.

The importance of these air-borne fungus spores as a cause of allergic conjunctivitis, nasal allergy and asthma cannot be too strongly emphasized. In the central states area we have found them to be the cause of respiratory allergy during the spring, summer and early fall, in a significant number of cases. These patients may or may not be sensitive to pollen; as a rule they are not, but have been considered as pollen-sensitive by a number of observers. In most instances, however, skin reactions to pollen were considered as borderline or negative. In the diagnosis and treatment of these cases we have employed an extract of feed-mill dust such as that described by Wittich.<sup>35,36</sup> This dust contains all the spores noted on slides exposed for making the pollen counts. Positive skin reactions to this extract have been consistent, and treatment with small doses has resulted in most satisfactory relief. In a number of cases presenting a rather typical history of the vernal type of conjunctivitis, the response to mold therapy was also satisfactory.

### ALLERGY AND PEDIATRICS

Clinical papers on allergy in children by Deamer,<sup>7</sup> Long,<sup>20</sup> Criepe,<sup>4</sup> Miller<sup>25</sup> and Marks<sup>21</sup> emphasize the importance of the diagnosis and treatment of respiratory allergy. Attention is called to the fact that symptoms simulating the common cold, characterized by sneezing, nasal obstruction and discharge are frequently overlooked as allergy and treated as infection. There should be no difficulty in making the distinction between allergy and infection if the nasal secretions are examined for the presence of eosinophiles or neutrophils. It is important to consider the common cold, however, as a complication of a nasal allergy. During a cold there may be an absence of eosinophiles. Follow-up examinations in these cases will reveal an eosinophilia after the cold has subsided. Some of these observers call

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attention to the frequent unnecessary removal of tonsils and adenoids in these cases considered as infections. Chronic persistent cough in children is often a forerunner of asthma and should be carefully investigated from the allergic standpoint.

### THE NOSE AND PARANASAL SINUSES

Shambaugh<sup>31</sup> reports his observations on the differentiation of infectious and allergic rhinitis. In 102 consecutive cases of chronic nasal or sinusal disease which he reviewed, the condition was essentially nasal with secondary involvement of the sinuses in fifty-one. In forty-three of these there was response to allergic treatment. In the other fifty-one cases the disturbance was primarily sinusal and in thirty-six of these a response to treatment for allergy was obtained. He emphasizes that both the infection and the allergic condition must be treated in order to give maximum relief.

In the management of allergy as related to otolaryngology, Hansel<sup>15</sup> emphasizes the importance of diagnosis of nasal and sinus allergy as well as other associated manifestations. In the treatment of hay fever small doses of pollen extracts given subcutaneously or intracutaneously are recommended. Both pre-seasonal and co-seasonal methods may be employed. In the treatment of dust sensitives, small doses are also recommended, starting with a 1-10,000,000 dilution in small children, 1-1,000,000 in older children and in adults with severe symptoms. Most patients received satisfactory relief with maximum doses of .10 to .20 of 1-100,000 or .10 to .20 of 10,000. In only a few cases was a 1-1,000 dilution employed. On the whole, the skin tests as a means of determining the relative degree of sensitivity to dust was found unreliable. Very good results were obtained in cases in which the skin reaction was entirely negative. In general, the administration of weak or stronger doses was based upon the degree of clinical sensitivity or severity of symptoms. Weak dosage was employed in the severe cases and stronger dosage in the mild cases.

In the study of cases of so-called recurring sinusitis, bronchitis, colds or catarrh in Southern California, Smith, Goodhill and Webb<sup>32</sup> point out that such conditions are caused by an unrecognized or hidden pollen allergy. The pollen allergy problem in Southern California presents great difficulties owing to perennial pollen present in the air. They state that continual exposure to perennial pollens results in the development of a low-grade resistance which is not sufficient to prevent allergic symptoms but does result in minimum reactions to the usual skin tests. Perennial pollen treatment, including empirical treatment with the pollens indicated by the patient's history and environment when tests were inconclusive, was found to be of definite value.

In the diagnosis of pollen allergy, the skin reaction is considered a very reliable guide. Minimal or borderline reactions always present a problem in treatment. It is important to take into consideration the possibility of atmospheric mold sensitivity in those cases. If the patient's symptoms parallel the pollen count, treat with pollen extracts. If they parallel the atmospheric mold count, treat with molds. In some instances treatment with both may be indicated. According to our experience in the central states area, therefore, most of the questionable pollen cases have proved to be mold cases.

In a group of eighty cases of chronic maxillary sinusitis in which an antrum window operation was performed, McHenry<sup>23</sup> reports that in twenty-one the infection was of dental origin and in twenty-three allergy was a factor. Among the allergy cases, eighteen were relieved of their sinus symptoms. In the entire group of eighty cases, sixty were considered as cured, twelve were relieved of symptoms, and in eight the results were unsatisfactory.

In a personal study of 250 patients who had had operations on the nose and sinuses, Hollender<sup>18</sup> found that the results were satisfactory in 65 per cent of the

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nasal cases and in 38 per cent of the sinus cases. According to the results reported by 154 rhinologists in a reply to a questionnaire, the "cures" reported were 71 per cent for nasal surgery and 42 per cent for sinus surgery. Hollender finally concludes that the chief factors in unsuccessful operations are: inaccurate diagnosis; neglect of allergic factor; failure to appreciate the importance of systemic diseases, such as diabetes, syphilis or tuberculosis; too hasty surgical intervention; poor surgical technique or incomplete operations; and inadequate postoperative care.

According to the observations of Urbach and Gottlieb,<sup>33</sup> vasomotor rhinitis was encountered in 38 per cent of 379 cases of asthma. This percentage seems far too low. In children with asthma we found the incidence of nasal allergy almost 100 per cent. In adults with asthma, the incidence of nasal allergy is about 90 per cent. These estimates were corroborated by positive cytologic findings in the nasal secretions. Nasal allergy associated with asthma is often very mild, so much so that the patient does not complain about it, yet a diagnostic eosinophilia is present.

After fourteen years' study of nose and throat problems in relation to asthma, Weille<sup>34</sup> concludes that the rhinologist cures asthma in about 10 per cent of the cases referred to him. Symptoms are relieved in about 40 per cent for shorter or longer periods of time and no results are obtained in the remaining 50 per cent. The cases seen by the rhinologist, he states, represent the failures of the allergist to a great extent and are therefore a special group. For better results, a closer collaboration between the rhinologist and the allergist and a better understanding of the relation of sinusitis to asthma is advocated.

### DRUGS

During the past few years a number of synthetic ephedrine-like drugs have been developed for the treatment of respiratory allergy. In general, an attempt has been made to eliminate those factors which cause a rise in blood pressure, palpitation and nervousness.

Friedman and Cohen,<sup>13</sup> in reporting the use of a new synthetic ephedrine-like drug—nethamine—in the treatment of hay fever and asthma, state that of twenty-three cases of hay fever, fourteen were improved, and of twenty-three cases of asthma eleven or 48 per cent were improved. The incidence of such symptoms as nervousness and insomnia was definitely less with nethamine than with ephedrine, while nethamine was at least equally as effective in relieving symptoms. The heart rate and blood pressure were unaffected.

Fabricant and Van<sup>11</sup> report their observations of the use of pricine hydrochloride, a new imidazoline derivative, 2 naphthyl-methyl imidazoline. It is crystalline and readily soluble in water or normal saline. In animal experiments it was found that a 0.1 per cent solution had no detrimental effect on ciliary activity. In normal subjects it caused no alteration in the pH of the secretions. It caused no irritation of the mucous membranes or any of the toxic side-effects as sometimes noted with ephedrine.

Scott<sup>30</sup> reports two cases, both in children, in which severe reactions to ephedrine occurred, although both patients had been treated previously with ephedrine without ill effects. One patient, a girl aged twelve years, had used a nasal spray of 2 per cent ephedrine and had also taken it internally without ill effects. Later, following the use of 1 per cent ephedrine in the nose, she developed a severe reaction of chilliness, dryness of the throat, palpitation and restlessness. The second patient, a boy aged six years, who had hay fever and asthma, had taken ephedrine internally in doses up to  $\frac{3}{8}$  gr. with  $\frac{3}{4}$  gr. amytal without ill effect. Later, during an acute infection with asthma, the same dosage was followed by a severe reaction characterized by restlessness, anxiety, thirst, rapid pulse and respiration. Scott stated that such violent reactions to ephedrine in children normally tolerant to the drug seem inexplicable, but point out the necessity for caution in the administration of ephedrine.

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Although the above reactions to ephedrine might be considered of an allergic nature, it also appears that they may simply have been the result of overdosage. A dosage of  $\frac{3}{8}$  of a grain of ephedrine is very large for a child; even many adults will not tolerate it. In general, an average dose of  $\frac{1}{8}$  gr. for a child and  $\frac{1}{4}$  gr. for an adult is sufficient. In some instances large doses are required for effectiveness and may be well tolerated.

Girling<sup>14</sup> reports his observations on the use of histamine in 120 cases which included seventy-three cases with postnasal drip with other evidence of allergy such as intermittent nasal obstruction; fourteen cases of nasal allergy with conductive deafness; twenty cases of lower half headache with nasal symptoms; six cases of asthma; five cases of dermatitis and two cases of laryngitis. Intracutaneous tests were made with 0.01 c.c. of a 1-100,000 dilution of histamine diphosphate. An area of erythema over 35 mm. in diameter was considered a positive reaction. In the treatment of positive reactors, the dilutions used were: 1-100,000, 1-75,000, 1-50,000, 1-25,000 and 1-10,000. When the first evidence of reaction appeared, the dosage used was reduced to two-thirds of the last dose; this was further reduced if reaction continued. From twenty-five to forty treatments were given. After the course of treatment, the skin reactions were greatly reduced or negative. Of seventy-three cases of nasal allergy, seventy were completely relieved; of the fourteen cases of nasal allergy with conductive deafness, five were completely and eight partially relieved; fifteen of twenty lower half headache cases were entirely relieved; of six cases of asthma, five were completely relieved. Four of five cases of dermatitis were relieved. Both of the cases of laryngitis were completely relieved. Girling concludes that it remains to be determined whether these results are permanent.

Criep<sup>3</sup> reports the case of an allergic patient who developed nasal allergy and asthma following the topical application of argyrol. A positive scratch reaction was noted with a 1 per cent solution. An intracutaneous test with this solution resulted in a severe local and a mild constitutional reaction. Ophthalmic and passive transfer tests were also positive. Tests with several other preparations of mild silver protein were negative. The protein molecule associated with the argyrol was believed to be the sensitizing factor. Criep is of the opinion that argyrol may be a frequent cause of sensitization and may be the cause of the discomfort some patients experience from its use.

Kauvar and Mont<sup>19</sup> report their observations on a study of 127 patients with common colds, of whom seventy-five were treated symptomatically and fifty-two with sulfonamides. The usual dosage of the sulfonamides was 2 gm. initially followed by another 2 gms. in two hours, then 1 gm. every four hours. Treatment was continued from three to eight days. No complications were noted. The sulfonamide-treated patients averaged 5.01 days and the control group 5.26 days in the hospital. From these studies it was concluded that the use of sulfonamides in the treatment of mild upper respiratory infections is not justified. Toxic reactions or sensitivity may develop, thus possibly making it impossible to use in the case of the development of a more serious illness. They recommend the use of sulfonamides, therefore, only in the complicated cold cases.

Recent reports on the use of the sulfonamide drugs locally or generally in the treatment of the common cold have been controversial as to whether they are or are not effective. Davis<sup>6</sup> reports his observations on the treatment of 157 cases treated by ordinary symptomatic drugs and compares the results with a group of 162 in which sulfathiazole was given orally in 1 gm. initial doses followed by  $\frac{1}{2}$  gm. every four hours. A control group consisted of 187 men and women. Treatment was given for three days. At the end of that period 70.3 per cent of those given sulfathiazole were cured and 22.3 per cent were improved. Thirty-nine per cent of those given symptomatic treatment were cured, 35 per cent improved. Of the control group, 47 per cent were cured and 29 per cent improved. The 162 treated with

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sulfathiazole lost thirteen days from work while in the control group of 187 ninety-six days were lost. There were a few reactions to sulfathiazole, such as nausea, eight cases; headache, five cases; dizziness, five cases. Davis concludes from this study that sulfathiazole treatment of common colds in industrial workers results in an important saving of working time.

Ebert<sup>10</sup> reports his results in the treatment of acute rhinitis in ninety-two patients from the use of sulfathiazole powder insufflated into each nostril daily or every other day. Relief of symptoms was almost instant and there was no irritation. The amount of sulfathiazole powder insufflated with each treatment averaged 0.0164 gms. for each side of the nose. Each patient received an average of three and one-half treatments so the total amount of drug used was only 0.12 gm. None of the patients showed the slightest toxic effect.

Our experience in the use of sulfathiazole in the treatment of the common cold is in agreement with that of Davis and of Ebert. The treatment is more effective when used early, that is, the first or second day. It should be administered about three times a day and should not be continued more than three or four days. Continued use for longer periods seemed to set up a great deal of irritation in some cases. Overtreatment might induce local and perhaps general sensitization. A great deal of caution should be exercised in treating allergic patients with colds because of possible sensitization. If a patient has had previous toxic or sensitization manifestations from the administration of sulfonamides, it should not be used in the nose, for even the small amounts introduced can cause toxic symptoms and allergic manifestations, especially dermatitis.

### THE EAR

Merica<sup>24</sup> discusses his findings in 135 cases of vertigo due to tubal obstruction. Many of the patients had associated acute or chronic disease of the sinuses or ears. In fifteen instances the condition was associated with colds. Some patients obtained immediate relief from severe vertigo after inflation of the eustachian tubes. Some patients derived permanent relief from one inflation. Others had recurrence of symptoms and required repeated treatments. Some patients with eustachian tube obstruction proved to be allergic and improved when the offending allergen was recognized and eliminated. Patients with a low metabolic rate had improved tubal patency after the administration of thyroid.

Noun<sup>28</sup> reports the occurrence of chronic otorrhea caused by food sensitivity in two children, aged eight and fifteen years. Positive skin reactions were demonstrated with several foods by direct and transfer tests and were corroborated clinically. The otorrhea subsided following the avoidance of the offending foods. Re-introduction of the foods caused an exacerbation of the otorrhea. It was suggested that the membranes of the middle ear were the site of the allergic reactions. In both patients a perforation of the ear drum had existed from a previous otitis media. No cytologic studies were made on the discharge from the ears. Both children had nasal allergy.

Although it is possible that the middle ear may be the site of an allergic reaction, in cases of the type reported in which there is an old perforation of the drum associated with a nasal allergy, it is difficult to determine whether the secretion in the middle ear arises from this site or comes from the nose as a result of blowing. With the subsidence of the nasal allergy the aural discharge should also subside. We have observed a number of cases of this type in which an otorrhea subsided under similar conditions. The discontinuation of nose blowing may also result in improvement or cure.

### THE EYE

Bab<sup>1</sup> reports his observations on allergy of the eye in a group of eighty-three cases, in forty-one of which there was edema of the eyelids. The etiologic agents



varied greatly and included sleeping pills (phanadorm) in one case; stewed cherries in another; strawberries in two others; and mechanical irritation such as that produced by plucking the eyebrows, squeezing the margin of the lid to straighten the lashes and dyeing the eyebrows.

O'Brien and Allen<sup>29</sup> report their observations on the diagnosis and treatment of allergic keratoconjunctivitis. This condition is characterized by recurring attacks of redness and swelling of the eyelids, accompanied by itching, lacrimation and discharge. A local eosinophilia, they state, may or may not be demonstrated. In one of the cases reported orange was the offending allergen. A patch test with orange peel was positive and the ingestion of orange was followed by keratoconjunctivitis. In another case butyn was the cause. In three additional cases the causes were hydrous wool fat in an ophthalmic ointment, a proprietary inhalant, and a fur coat, respectively.

Morrison<sup>27</sup> reports a case of chronic catarrhal conjunctivitis aggravated by the application of an ointment of sodium sulfathiazole and sulfathiazole. Discontinuation of its use resulted in a remission and re-application caused an exacerbation. The base was found to be innocuous.

Marton<sup>22</sup> reports four cases of severe vernal conjunctivitis caused by pollen sensitivity. None of the patients had nasal symptoms. Two patients failed to show reactions to pollen. One reacted to grass and ragweed and one to grass, hickory and faintly to ragweed. All four patients were given intensive treatment with pollen extracts with good results.

In cases of this type it is important to consider atmospheric molds as a possible factor.

Brown, Irons and Rosenthal<sup>2</sup> made the observation that workers in laboratories producing cultures of tubercle bacilli noticed that systemic reactions resulted when the fumes from boiling suspensions of dead tubercle bacilli were inhaled. After repeated exposures, cutaneous sensitivity to tuberculin became markedly decreased. In two cases reported, recurrent tuberculous iritis had been present for many years. In neither patient could foci of infection be found. Both reacted strongly to Mantoux tests. Both patients became free of symptoms after repeated inhalation of the fumes from boiling suspensions of tubercle bacilli. A slight recurrence of iritis once followed the direct exposure of the eyes to the fumes. Animal experiments showed that sensitized guinea pigs could be desensitized by the repeated inhalation of the fumes.

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# Correspondence Items

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## Contact Dermatitis Due to Permanent Wave Process Additional Notes

Dr. Ralph Bowen reported in the January-February ANNALS three patients with contact dermatitis due to a "cold" or "heatless" permanent hair wave process. Since that time, Dr. Bowen received the following information from Dr. Louis Schwartz, Medical Director and Chief of the Dermatoses Section of the U. S. Public Health Service, concerning cold wave solution:

According to a letter received by Dr. Schwartz from the National Mineral Company of 2628-58 North Pulaski Road, Chicago, Cold Wave Solution is made with "ammonium salt of thioglycolic acid as the essential ingredient. The compound is of a high state of purity and is accurately controlled to a pH of 9.4 with ammonia. The concentration of the thioglycolic acid proper is 6½ per cent."

Dr. Schwartz comments: "From this information, dermatitis from the Cold Wave Solution may be produced either by the fact that it is alkaline or by sensitization to thioglycolic acid. The latter is more tenable because of the fact that your patients had no difficulty on the first application but developed a violent dermatitis on the second. They became sensitized by the first application." Dr. Schwartz states that a proper dermatological study advocated by his Section when testing such products is to do patch testing on 200 individuals and ten days after removal of the first series of patches, retest them to see if any have been sensitized. The person performing and interpreting such patch tests should be an experienced dermatologist.

If there are any more cases of dermatitis of this nature, THE ANNALS would be pleased to have comments for publication.

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## Allergic Bronchitis

To the Editor:

In enjoyed reading the article on "Allergic Bronchitis" by Thomas and Taylor.\* My interest was attracted to the statement in their summary that "Physical examination is not diagnostic, nor are laboratory procedures . . ." I trust that their omission of mention of studies of the sputum for eosinophiles was an oversight. The differential diagnosis of chronic cough may often be difficult and it is fortunate that our armamentarium includes a laboratory procedure as simple and as informative as the examination for sputum eosinophilia. This allows us in most cases to make the diagnosis of allergic bronchitis with precision, rather than by exclusion. In the investigation of all suspected allergic disease of the respiratory tract, this diagnostic procedure should be a part of the routine examination.

With best regards, I am,

Sincerely,

ALBERT R. ZOSS, Captain, M.C.

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\*See page 185, November-December 1943 issue

# ★ In Memoriam ★

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## WARREN TAYLOR VAUGHAN, M.D.

Dr. Warren Taylor Vaughan died suddenly April 2, 1944, in Richmond, Virginia, a victim of coronary occlusion. He was born in Ann Arbor, Michigan, on February 22, 1893, the son of the late Dora Catherine (Taylor) Vaughan and Victor Clarence Vaughan, who was well known in the field of immunology and was Dean of the Medical School of the University of Michigan from 1891 to 1921.

Warren Taylor Vaughan received the following degrees from the University of Michigan: B.A. in 1913, M.D. in 1916, and honorary M.S. in 1941. On June 21, 1917, he was married to Emma Elizabeth Heath, and they had four sons, Victor, Clarence III, Warren Taylor, John Heath, and David DuPuy. He was house officer of the Peter Bent Brigham Hospital, Boston, 1916-17; assistant in preventive medicine and hygiene, Harvard Medical School, 1919-20. After 1920 he was in the practice of internal medicine and specialized in allergy; he was also director of the Vaughan-Graham Clinic in Richmond, Virginia. During World War I he served as 1st Lieutenant and advanced through the grades to Lieutenant Colonel, U. S. Army, Chief of Medical Service, Camp Hospital 41, A.E.F.

Dr. Vaughan also held important positions on various committees dealing with national problems; the organizations of which he was a member included the following: Fellow A.A.A.S. (council since 1938), member Medical Society of Virginia (vice president, 1931-32), Southern Medical Association, American Medical Association, American Society of Clinical Pathologists, American Association for the Study of Allergy (secretary-treasurer, 1928-38; president, 1939), Society for the Study of Asthma and Allied Conditions (president, 1938-39), American Rheumatism Association, Society of Investigative Dermatology, International Society of Gastro-enterology, Institute of Practice of Medicine, Barcelona, Spain (honorary), Society for the Study of Allergy, Argentine (honorary), Virginia Academy of Science.

Dr. Vaughan contributed much to medical knowledge and to the advancement of the subject of allergy. He was the author of several books, including *Influenza, An Epidemiologic Study*, 1921; *Allergy and Applied Immunology*, 1931; *Practice of Allergy*, 1939; *Primer of Allergy*, 1939; *Strange Malady*, 1941. Editorial positions included editor-in-chief, *Journal of Laboratory and Clinical Medicine*; associate editor, *Journal of Allergy*, until January 1, 1944; membership on the editorial board of the *American Journal of Digestive Diseases and Nutrition*, *American Journal of Clinical Pathology*. Formerly, he was a member of the editorial board of *Review of Gastro-enterology*, *American Journal of Syphilis*, and collaborating editor *Folia Clinica Chimica et Microscopica* (Bologna, Italy). He also contributed more than 150 articles to current medical literature, including the *Encyclopedia Americana* and *Oxford Medicine*.

More specific contributions to the subject of allergy included studies in food allergy, particularly as related to the leukopenic index and genetic classification of foods. His *Practice of Allergy* is appreciated by all men interested in allergy as one of the outstanding texts and reference books and in itself may be considered an encyclopedia. Dr. Vaughan was an untiring clinician and investigator. His opinion on all subjects related to allergy has been respected, and his efforts for the advancement of this subject have been unlimited. The patient understanding and aid of his wife in assisting him with many of his manuscripts as well as in his investigative work enabled him to accomplish much that otherwise would have been more difficult. His work as a teacher as well as his appreciation for the

## IN MEMORIAM

advancement of allergy is evidenced by the number of men that he trained at his clinic in the specialty of allergy and in the time he devoted to the teaching of technicians. He ingeniously applied his hobby of photography to demonstrations of his clinical cases and in his scientific publications.

In all personal relationships, Dr. Vaughan was stimulating; he thought straight. He was original, practical, and scientific in his approach to all new problems. Under pressure he was efficient, ingenious, and resourceful—a leader and an inspiration to all who worked with him. He will be sorely missed not only by his family but also by a wide circle of personal friends and clinicians, including many active clinical investigators throughout the country. His name will stand out as one of the leading American men of science and allergy.

J. WARRICK THOMAS

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### Allergy in Otolaryngology and Ophthalmology

(Continued from Page 172)

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### DIAGNOSIS OF HYDATID DISEASE. *Bull. Lederle Lab.*, 11:29, (Nov.) 1943.

Hydatid disease or echinococcosis, is an infection with the larval or hydatid stage of a tapeworm, *Echinococcus granulosus*. It was the first parasitic infection for which diagnostic immunological tests were successful. These tests depend upon the presence of antibodies in the circulation or tissues of the patient. Precipitin, complement fixation and skin tests all have been utilized in diagnosis. Antigens from heterologous cestodes give a reliable "non-specific" positive immediate reaction in about 95 per cent of patients harboring hydatid cysts. Intradermal tests are performed with 0.01 c.c. of 1:100 tapeworm extract. Positive skin test should be interrupted with regard to history, symptoms and laboratory findings including stool examinations to rule out intestinal cestode infestations.

L. J. H.

# News Items

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## FUNDS FOR RESEARCH IN ALLERGY

In accordance with the policy established by the College in 1942, a Research Foundation has been firmly established by the College. The College initiated the first Fund to be used for encouraging research in allergy by appealing to 100 Fellows of the College who are able and willing to do so to contribute \$50 each towards the Fund and that such contributors are to constitute an Honor Roll. The voluntary response of members has been very satisfactory.

On February 28, 1944, Marcelle Cosmetics, Inc., made their first annual gift of \$500 to the College to be known as the Marcelle Research Fund. The grant is to be repeated each year for a period of five years. This Fund shall be administered by whatever officers or agency the College shall designate, the money to be used in such research in the field of allergy deemed by the administrators worthy of support. Members of the College who have been selected for the administration of this Fund are nationally recognized personalities in allergy and have had extensive experience in research problems.

The College wishes to express its sincere appreciation to the Marcelle Cosmetics, Inc., for this manifestation of their confidence and high esteem in the organization, when accepting such a worthy gift.

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Captain Alfred L. Seal (MC) has been retired to the inactive reserves and has opened an office in the Beverley Hills district in Los Angeles. His home address is 1844 Wooster Street, Los Angeles 25, California.

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The Southwest Allergy Forum held a very satisfactory and enthusiastic two-day informal round table discussion on practical allergy subjects at Jackson, Mississippi, April 15 and 16. The program was varied, and the leaders and coördinators represented outstanding allergists of the Southwest.

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The College library gratefully acknowledges reprints from many of the Fellows the past two months, including various monographs and reprints from South America. The latter include "Anemopolinologia Aplicada," by Dr. Miguel Augustin Solari, of Buenos Aires; "Las Manifestaciones Alergicas des Aparato Urinario," and "Sobre Alergia Fisica," by Dr. Mariano R. Castex, of Buenos Aires; "Alergia Polinica" Separata do Brasil, by Dr. O. Oliveira Lima, of Rio de Janeiro; "Polinosis," by Dr. Leopoldo H. Ballesterio and Dr. Juan V. Monticelli, of Buenos Aires.

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The College membership certificates are being mailed now, as rapidly as completed. Certificates will not be sent abroad to those in the Service since they are framed, but will be sent to the home address. Those members abroad who do not have a home address at present will have their certificates held until further instructions are received from them.

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The College is very grateful to Almay, Inc., New York, for furnishing the cocktail hour preceding the informal dinner of the Annual Meeting, Saturday evening, June 10, Palmer House, Chicago.

## AUSTRALIA

Dr. Bernard Riley, Harley, 143 Macquarie St., Sydney, N.S.W., Australia, has qualified as an Active Fellow of the College. Dr. Riley is Medical Officer, in charge of the Allergy Clinic of the Royal North Shore Hospital of Sydney.

# BOOK REVIEW

THE 1943 YEARBOOK OF DERMATOLOGY AND SYPHILOLOGY. Edited by Marion B. Sulzberger, M.D., and Rudolph L. Baer, M.D., 584 pages, 72 illustrations. Price—\$3.00. Chicago: The Year Book Publishers, 1943.

Dr. Fred Wise, former editor of the Year Book of Dermatology and Syphilology, has retired from this position to be succeeded by his co-editor Dr. Marion B. Sulzberger (Comdr. MC, USNR). Dr. Sulzberger has chosen Dr. Rudolph L. Baer as his assistant editor. In line with rulings by the War Productions Board, the publishers have introduced the volume with a lighter weight paper, printing more words to the page and reducing the margins. The result is a very compact, durably bound, easily read volume, without sacrificing any of the contents.

Dr. Sulzberger, also noted for his clear concise expression, admirably succeeds in following the precepts of Dr. Wise. The editor recognizes the proper importance of the role of immunology and allergy in dermatologic diseases. However, the entire range of skin diseases, based upon recent authoritative literature, is adequately presented with our present-day knowledge of their recognition and management.

A very complete practical guide for skin tests and other immunologic procedures in common dermatologic and venereal diseases is given in the opening chapter. Throughout the book cutaneous hypersensitivities to topical applications and internal medication are stressed. The therapy of nonvenereal diseases and x-ray and other physical therapy are discussed in detail. Eczema, urticaria and allergy; the hematogenous dermatoses; miscellaneous dermatoses; fungous and other infection of the skin; tumors; venereal diseases and therapy, together with a chapter on investigative studies, are completely presented.

The omission of nonessentials makes the book a compact manual of skin diseases which every practitioner should always have at hand.

—F.W.W.

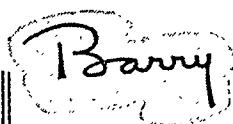
## Attention Please!

### IMPORTANT NOTICE

Hotel and traveling reservations for the Annual Meeting should be made NOW.

Consult map of Chicago loop district convention hotels, pages 132-133, for details.

Also see convention number, *Journal of the American Medical Association*.



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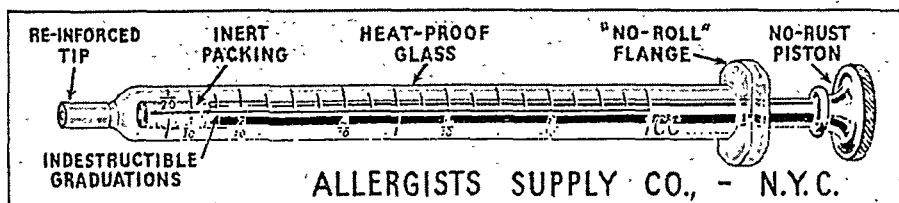
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Vol. 2 No. 4

# ANNALS *of* ALLERGY

Official Journal of the  
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**Annals of Allergy** is published bimonthly by the American College of Allergists. The contents of the journal consist of contributions in the field of diseases of allergy, book reviews, a current bibliography, editorials, case reports, new suggestions, questions and answers, news items and matters concerning the affairs of the American College of Allergists.

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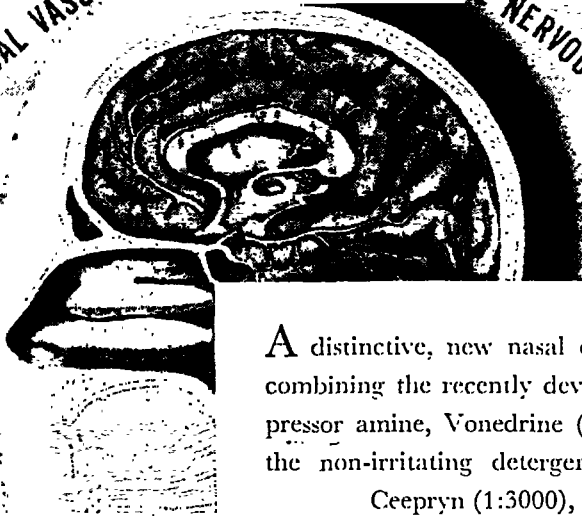
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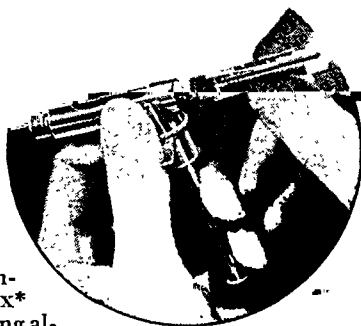
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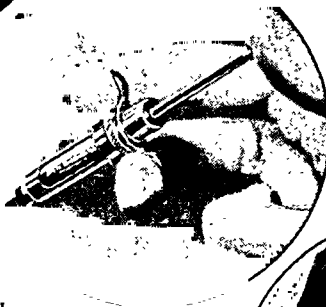
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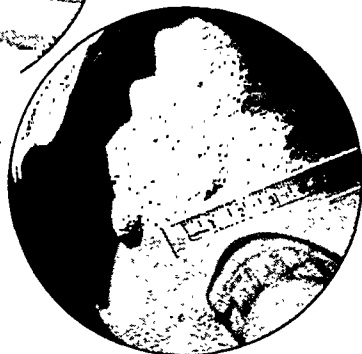
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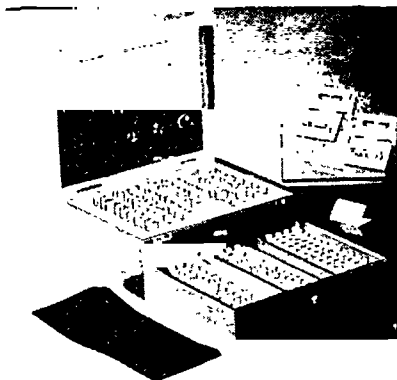
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# ANNALS of ALLERGY

*Published by the  
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Volume 2

July-August, 1944

Number 4

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## QUALITATIVE DIFFERENCES AMONG CANINE DANDERS

SANFORD B. HOOKER, M.D., F.A.C.A. (Hon.)  
Evans Memorial, Massachusetts Memorial Hospitals, and  
Boston University School of Medicine  
Boston, Massachusetts

MY deep appreciation of the honor of receiving your invitation is unfortunately tempered by my lively realization that I can offer so little in return. My subject was virtually picked out for me despite my protestations and expostulations that the available data on differences between the atopic excitants derived from different breeds of dogs are meager and fragmentary.

Perhaps the topic was deemed somewhat appropriate at this time because of the College's present forward-looking action in organizing a Section of Veterinary Allergists.

Certainly the dog can easily be brought into pertinent relation with the various fields of knowledge that surround allergy as they appear in the insignia of the College. Literature, both romantic and scientific, abounds in references that establish the dog's connection with many arts and sciences.

"I pray thee let me and my fellow have a haire of the dog that bit us last night" suggests Immunology. Under Physiology we recall Pavlov's experiments on the conditioned reflex. The dog-tooth violet, dogbane, dogwood, and a kind of grass called *Cynosurus* remind us of Botany.

The connection with Entomology is so obvious that I quote the following statement only to give the author his rightful due; it was David Harum, not Mark Twain, who remarked "They say a reasonable number of fleas is good for a dog—keeps him from broodin' over bein' a dog." In the field of Bacteriology, studies of canine distemper opened the way toward solving the problem of human influenza. When we're "sick as a dog" we think of Medicine.

---

Address of the Guest of Honor presented at First Annual Meeting, American College of Allergists, Chicago, Illinois, June 10, 1944.

Further to exhibit canine versatility we may bring in Pharmacology—"Throw physic to the dogs; I'll none of it"; Meteorology—"dog-days" and "raining cats and dogs"; Politics—"things are going to the dogs"; "dog in the manger"; "A dog starved at his master's gate predicts the ruin of the state." This could go on for a dog's age, but eventually I'd land in the doghouse.

My interest in the possibility of differentiating breeds of dogs by the techniques of allergy was aroused just six years ago when I saw a patient who had a very severe attack of asthma two days after he had acquired a French poodle. For a number of years immediately preceding, he had had an English bulldog as a close companion and there had been no hint of any allergic trouble from this source. The poodle was removed to a friend's house and the patient's house was cleaned. The patient returned from the hospital, where the attack had promptly subsided, and had no more asthma except for a mild attack shortly after his friends, minus the poodle, had visited him.

His physician scratch-tested him with a stock preparation of canine dander; no reaction occurred. I prepared an extract of combings from the poodle and did endermal tests with it and with a stock extract (Lederle) prepared from a pool of hair from many dogs of different breeds, the material having been collected in the Veterinary School of Cornell University. There was no reaction to the stock extract in a concentration of 0.1 mg. N/ml. Reaction was strong to the 0.01 concentration of poodle-extract and definitely positive to the 0.001 strength. These and some other selected contrasting reactions are shown in Chart 1. The identical stock extract was active in the skins of many other dog-sensitive subjects even in test-doses of 0.01  $\mu$ g (0.01 ml. of 0.001 concentration). This patient (Web) also reacted moderately to extracts from Alaskan malamute, American shepherd, Chow, Siberian husky, and a hybrid  $\frac{1}{4}$  wolf,  $\frac{3}{4}$  husky; his reaction to wolf was very feeble; boxer and dingo salivas evoked no response whatever.

The chart also shows other rather remarkable differences in the reactivities of different subjects to the same extracts. Note that Meu reacted well to jackal saliva 0.001 whereas Web and Ron were negative to a hundredfold stronger concentration. This cannot be ascribed to Meu's quantitatively greater *general* sensitivity; actually Web was more sensitive to poodle than was Meu, as shown by tests with weaker dilutions.

When using a technique so coarsely quantitative as direct endermal testing, one should not be too deeply impressed by differences (or similarities) among reactions to extracts whose concentrations may vary fivefold or even tenfold. By "concentration" I refer to active excitant; the nitrogen-content is merely a convenient symbol to designate dilution. But, when subjects exhibit a diversity of response that extends over a hundredfold (10,000 per cent) or greater range of concentration, then

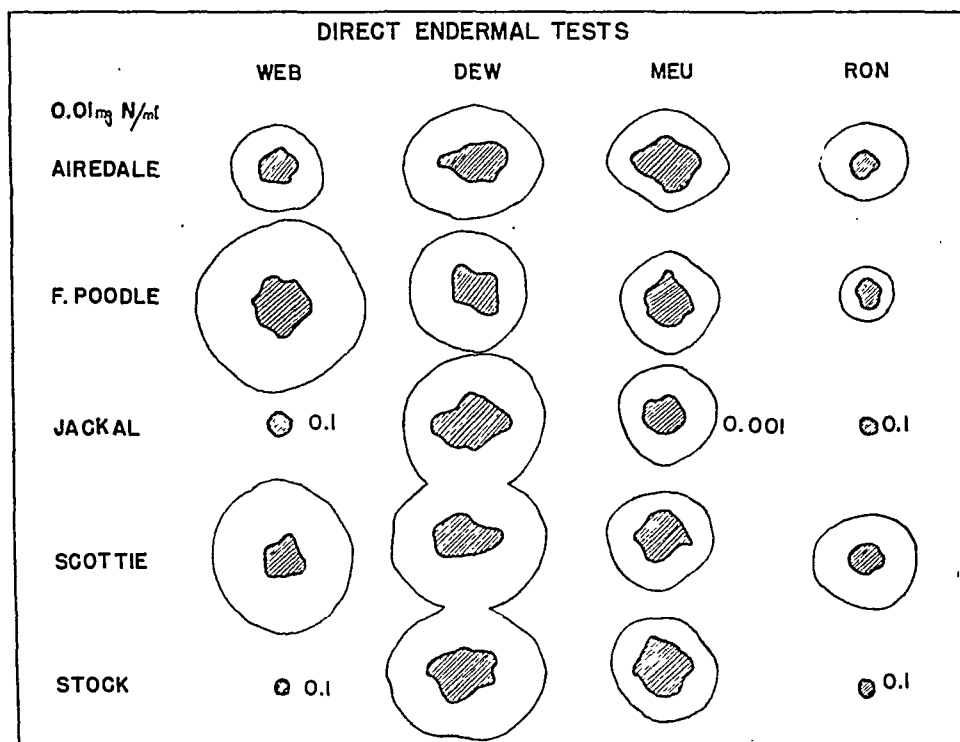


CHART 1.

we must seek an explanation involving qualitative as well as quantitative factors.

The logic is simple. If we assume the presence of a single atopic excitant common to the danders of different canine breeds, and if we so adjust the concentrations of two extracts that they elicit equal responses in a sensitive patient, then we must expect all other test-subjects to give reactions that are *parallel, i.e.,* strongly positive, weakly positive, or negative. Our failure to observe this parity of response indicates the presence of multiple or at least dual excitants in some extracts.

Patients' experiences are another source of information, although their observations should be considered as testimony rather than evidence. It is the general impression that short-haired dogs cause less respiratory allergy than long-haired ones. This is probably true but is plausibly ascribable to a difference in the amount of dander inhaled under conditions of ordinary exposure. Of course, there are no standard conditions of exposure; length of time, size and activity of the dog, frequency of grooming, number of hours the dog is in the house—these combine to form a set of variables difficult to control. However, many patients voluntarily or upon inquiry state that their clinical sensitivities are not the same to different breeds of long-haired dogs, and one patient tells a pretty convincing story. She is the wife of the Dog Constable in a Rhode Island

city; he frequently brings many different varieties of the residents of the pound to her home.

"I am very fond of dogs, and therefore take a particular interest in all of them, but have noticed that every time he has brought home a spitz or toy spitz my reaction has been very, very definite. I found I could not go near them without becoming very uncomfortably close to asthmatic spasms, therefore, I naturally have learned to keep away from that breed . . . the same thing happened with every spitz I came in contact with.

"The point is, I have had a cocker spaniel for the last seven years, in the house with me practically all the time, yet I am free from asthma for a period of four or five months each year, which proves, I think, that my spaniel does not affect me in any way."

In 1936, three years before this letter was written, I had found this patient's skin to be reactive to ragweed, dog, house-dust, and feathers. She later observed that the eating of grapefruit promptly brought on severe asthma. Dust-precautions, abstinence from citrous fruits, and treatment with ragweed "serum" have resulted in marked amelioration of her symptoms.

Two pertinent comments can be made. Cockers have furnished some of our strongest and apparently most multivalent extracts; when a cocker shakes himself in the slanting rays of sunlight, so that Tyndall's phenomenon is so simply and strikingly manifested, no one can doubt that this kind of dog contributes powerfully to the particulate pollution of the atmosphere.

A third source of information is the result of tests for cross-neutralization of reagin or sensitizing antibody by extracts from various breeds. I have made a few crude pilot-experiments of this kind; the results, although consistent with the postulate that qualitative differences exist, are not offered as proof that such is the case. They suffice, I think, to indicate the desirability of a more extensive and systematic study using such necessary technological refinements as determination of minimal sensitizing doses of serum and minimal neutralizing doses of antigen for "homologous" serum—meaning the serum of a patient who is clinically allergic to his "homologous" dog.

Chart 2 shows the results of tests with serum from Dr. Gardner's patient in Aurora, Illinois. After treatment with a stock extract this patient acquired clinical tolerance to one of her dogs, a Scottie, but remained reactive to her boxer. It is evident that the stock extract had little if any neutralizing capacity, whereas the Scottie neutralized completely. Chart 3 shows similar results with a weaker serum from a patient whose clinical history I do not know. Note that here again Scottie abolished the serum's reactivity although the response to test in an unneutralized site was minimal. It would strain even my imagination to attempt an explanation of

# CANINE DANDERS—HOOKER


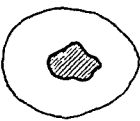

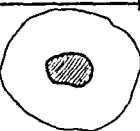



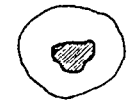











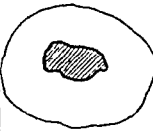

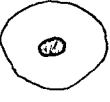





TESTED WITH	NORMAL SITES	PASSIVELY SENSITIZED SITES				
		SERUM G + SALINE	SERUM + BOXER 0.1	SERUM + STOCK 0.1	SERUM + POODLE 0.07	SERUM + SCOTTIE 0.1
BOXER 0.1						
STOCK 0.1						
POODLE 0.07						
SCOTTIE 0.1						
SALINE						

CHART 2.


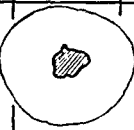

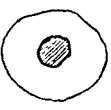

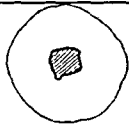









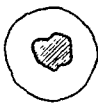

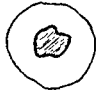



















TESTED WITH .01 ML	NORMAL SITES	PASSIVELY SENSITIZED SITES					
		SERUM K + SALINE	SERUM + BOXER 0.1	SERUM + JACKAL 0.1	SERUM + LEDERLE 0.1	SERUM + POODLE .07	SERUM + SCOTTIE 0.1
BOXER 0.1							
JACKAL 0.1							
LEDERLE 0.1							
POODLE 0.07							
SCOTTIE 0.1							
SALINE							

CHART 3.



this phenomenon but I record it because that is what happened and it may not be wrong.

Not enough work has been done to permit any estimate of the frequency with which patients exhibiting a high degree of discriminating selectivity may be encountered. Doubtless some or many breeds of dogs have an active common excitant. I have treated one patient with 'Scottie-extract'; she developed clinical tolerance to her Boston terrier and her cutaneous reactivities to both breeds diminished about equally.

The American Kennel Club recognizes over a hundred breeds of dog. For the purpose of thorough cutaneous testing it would be of obvious practical advantage to have a representative multivalent extract which might be compounded from the danders of relatively few breeds. Taking into consideration what is known of the ancestry of *Canis domesticus* it seems rather unlikely that any single breed would provide suitable testing material. Hybrids "... may show various combinations of the characters of the two parents, or exhibit new characters, or reversion to the ancestral ones." Irwin has clearly shown the development of new specific antigenic components in the erythrocytes of the offspring of cross-mated varieties of doves, and there is no reason to deny that an antigenic complexity of canine epithelium could be or has already been similarly generated.

Here arises a more academic, but nevertheless beguiling, question whether application of the techniques of allergy cannot add to our knowledge of biological relationships. "Systematic" serology, pioneered by Nuttall, critically refined and applied by Boyden, has used precipitins successfully in contributing confirmations and advances in zoölogical and botanical taxonomy. Simon has demonstrated that *some* allergic patients exhibit a remarkable general reactivity to mammalian sera. Perhaps the skin and sera of *some* dog-sensitive patients may prove to be such discriminating reagents as to further our knowledge of the evolution of modern dogs.

The seeker for information in this field is likely to be dismayed at the start when he encounters such scholarly opinion as that "The origin of the dog is wrapped in obscurity," or "is shrouded in the mists of antiquity." Darwin found the solution of dogs' ancestry most difficult:

"It is highly probable that the dogs of the world have descended from two good species of wolf (*C. lupus* and *C. latrans*) and from two or three doubtful species of wolves (namely the European, Indian and North African forms); from at least one or two South American canine species; from several races or species of the jackal and perhaps from one or more extinct species."

That there has been a multilateral descent is highly probable but a comparison of historical records and osteological and paleontological evidence allows the plausible assumption that four essential ancient strains gave rise to the dogs of the present day. These have been listed by Gwatkin as:

TABLE I.

TEST-EXTRACTS		THE FOUR "DOGS OF ANTIQUITY"
AIREDALE	HYENA	1. EGYPTIAN JACKAL-LIKE
ALASKAN MALEMUTE	JACKAL (S)	KITCHEN-MIDDEN DOG
BOSTON TERRIER	KERRY BLUE	<i>C. palustris</i>
BOXER (S)	4 NEWFOUNDLAND	2. ASIATIC (INDIAN). PARIAH-
1 CHOW	POINTER	DOG
1 COCKER	1 POODLE	<i>C. pallipes</i>
COLLIE	SCOTTIE	
COYOTE	SEALYHAM	3. EGYPTIAN (ASIATIC?)
DACHSHUND	SETTER (IRISH)	GREYHOUND
2 DINGO (S)	2 SHEPHERD	<i>C. simensis</i>
FOX	SIBERIAN HUSKY	
FOX TERRIER (wire haired) 1	SPITZ	4. TIBETAN MASTIFF
3,4 GREAT DANE	WOLF	<i>C. molossus</i>
1 HUDSON'S-BAY ESKIMO	¼ WOLF ¾ HUSKY	
(S) indicates saliva.		

1. An Egyptian jackal-like dog, which is the prototype of the Peat-pomeranian, Spitzhund, or kitchen-midden dog.

2. An Asiatic (Indian) pariah-dog, the prototype of the Bronze-age dog, the common hound or lurcher, the shepherd, and the dingo.

3. The greyhound-type, first record of which was found in the tomb of Aniten of the Fourth Dynasty (*ca* 3500 B.C.). It is easily credible that this kind of dog was domesticated in that early and most flourishing tract of human enterprise, the "Fertile Crescent," extending through Mesopotamia and Palestine to the valley of the Nile. The extensive habitable plains and the deserts made speed rather than scenting ability desirable in hunting dogs. The Borzois of the Russian steppes, the Persian greyhound and its cousin, or uncle, the Afghan, are very old species, streamlined, long-muzzled, and wasp-waisted.

4. The fourth dog of antiquity is *Canis molossus*, a huge coursing hound with drooping ears, derived from the thick-set Tibetan mastiff. These were the "dogs of war" much favored by the victorious Assyrians. By way of the Alexandrian conquest they reached Europe and have contributed many characteristics to the bulldog. The pug, St. Bernard, and Newfoundland are considered to be side twigs of this branch.

Table I lists my collection of extracts of canine origin and indicates the relation of some of them to ancient breeds. It shows, again, my casual and unsystematic approach to the problem. Particularly weak is the representation of the greyhound-type, the only example being the Great Dane, supposed to be a cross between a mastiff and greyhound. In self-defense I may say that once I did see an Afghan gazelle hound in the Fenway

and tried unsuccessfully to catch him for a grooming. It must have been a ludicrous spectacle!

The "dog's life" is various. In Egypt the dog was venerated; in many other ancient countries he was abhorred. The Old Testament regarded him as an unclean beast, traffic in dogs was an abomination; the Mohammedans' most scurrilous epithet bestowed upon a European or a Christian is "a dog." But in Egypt, "Figures of dogs appeared on most of the friezes of the temples. Herodotus said that the members of every family in which a dog died, shaved themselves—their expression of mourning—an Egyptian custom even in his day. The overflowing of the Nile was heralded by the appearance of the star Sirius over the horizon. The people then removed their flocks to higher ground and abandoned the lower pastures to the fertilizing inundation. They hailed the star as their guard and protector, called it the dog-star and worshipped it." This was serious.

On the other hand, Humboldt noted that the Peruvian dogs were made to play a singular part during eclipses of the moon, being beaten as long as the darkness continued. Among the Danes, before Christianity was established, on every ninth year at the winter solstice, a monstrous sacrifice of ninety-nine dogs was effected. In Sweden, on each of nine successive days, ninety-nine dogs were destroyed. And, long ago, the watchdogs of Rome were said to have been asleep on the celebrated occasion when the cackling of the geese saved the situation. The Administration was so enraged that the dogs in question were executed and a directive was issued that all dogs should be soundly thrashed once a year in commemoration of this shameful episode.

Finally, we must admit that the dog is a very peculiar animal: man's first ally, the most domesticated and intelligent, each entirely devoted to his master, distinguishes and defends his property, remains attached till death—not from constraint or necessity but from pure gratitude and friendship. These digitigrade fissipedal carnivora differ from each other much more than is the case with any other mammal, as in form, size, color, and length and kind of coat. They bury food, scratch and dig out live prey, eat herbs and grasses medicinally, diffuse a characteristic odor, wave their tails when excited, roll on their backs—preferably in carrion—to express pleasure. Their sardonic smile is an inimitable expression of mocking, derisive disdain. The way they greet each other, and their other habits of social intercourse are most unusual. Their notions of hygiene and sanitation are certainly extraordinary. Followers of the Cartesian method of developing a science without resort to experiment would have pondered over this considerable assemblage of characteristic canine traits and would have predicted that danders probably differ. Probably they would have been right.

## HISTOPATHOLOGY OF ECZEMATOID DERMATOSES

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IN a previous paper, by Dr. Jerome Glaser, certain dermatoses were considered and we hope to demonstrate their microscopic features. These are allergic or related diseases and therefore of considerable interest to this audience.

As many varied dermatoses may be eczematized or so become, this presentation will make no endeavor to consider those irrelevant to this society. Nor will any attempt be made to set down a classification of this group of dermatoses, nor to state, except in general terms, which do or do not belong to this category.

Four groups of diseases are under discussion: (1) contact dermatitis; (2) neurodermatitis; (3) nummular eczema; (4) eczema.

Realizing that this subject may not be too familiar to some, a few preliminary remarks may be helpful, for upon these elementary features and combinations of the same, the diagnosis and differentiation of these diseases depend.

*Histology.*—The normal skin is composed of: (1) the epidermis, (2) the derma, cutis or corium, and (3) the subcutis.

1. The epidermis is stratified squamous epithelium and consists of the rete pegs which extend downward between the papillary bodies, and the suprapapillary portions which overlie the papillary bodies.

For convenience only, the epidermis is divided into basal cell, prickle cell, granular, lucidum and horny layers. The basal cell or germinative layer is in direct contact with the underlying cutis. Its functions are to produce other cells, as prickle cells or cells of the adnexal structures, and also to form pigment (melanin). The stratum lucidum is most pronounced on the palms and soles. The keratohyalin zone (granular and horny layers), is not virile. The epidermis has no blood supply of its own, but it is bathed by a system of spaces separating the cells and through these spaces lymph, from the cutis below, circulates.

2. The derma, cutis or corium has a coarse and fine network of connective and elastic tissue. Within this framework blood and lymph vessels, muscles, nerves, appendages and some cellular elements are found.

For simplicity the cutis is divided into the upper, mid and deep portions. These zones are determined by the size of the blood vessels and by the structures present. Capillaries, composed of a single layer of endothelial

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From the Department of Pathology of the Skin and Cancer Unit of the New York Post-graduate Medical School and Hospital, Columbia University, Dr. George M. Mackee, director. Read and presented with Lantern Slide Demonstration by Dr. Charles S. Miller before the First Annual Meeting of the American College of Allergists (Instructional Course), June 10, 1944.

cells, are found in the papillary bodies and about the appendages. Arterioles are present in the upper cutis and the small arteries in the mid and deep cutis.

The sweat gland is in the deep cutis and sometimes in the fat, while the sweat duct extends upward from the glandular portion and enters into the bottom of a rete peg. The pilosebaceous apparatus consists of the hair root, the hair follicle, the hair and the sebaceous gland. The hair root is in the deep cutis, while the hair and the hair follicle extend through all three zones. The sebaceous gland is in the mid cutis.

3. The subcutis is composed of a fine network within the meshes of which is the fat. The large vessels and nerves are in this layer.

In the diseases considered here, neither the subcutis nor the deep cutis plays an important role. The epidermis and the upper cutis are mainly involved and in some instances the mid cutis.

*Inflammation.*—All inflammatory processes must originate in the cutis as the epidermis has no blood supply of its own. Inflammation is characterized by congestion, edema and cellular infiltration. One or any combination of these features may predominate.

Over such an inflammation the epidermis may or may not be involved. The epidermis is unaffected in many allergic dermatoses. These do not come under consideration here because to be "eczematized," we believe the epidermis must be involved in the process.

Therefore, the epidermis in the eczematoid dermatoses should show evidences of intercellular edema, spongiosis, vesicle formation, parakeratosis, acanthosis, or a combination of these. By acanthosis we mean a hyperplasia of the prickle cell zone following an underlying inflammation.

#### CONTACT DERMATITIS

This may be of two types, either serous or necrotic. Concerning the former there have been two schools of thought, one holding that the edema comes from the surrounding lymph of the epidermis, the other claiming that in some way the offending agent causes a reaction in the underlying cutis and the edema develops following this reaction. The question is not settled and it is unnecessary here to go into the pros and cons on both sides.

In the serous variety of contact dermatitis, the vesicles are on the surface of the epidermis (Fig. 1). While there may be one, usually there are many. These may be small, but occasionally they are large. There is little intercellular edema or spongiosis about the vesicles, nor is there any appreciable evidence of edema in the rest of the epidermis. In the upper cutis and in the subepidermic zone the vessels are dilated, there is some interstitial edema and a moderate diffuse cellular infiltration of small round cells and wandering connective tissue cells.

In the primary irritant type of reaction the vesicles are small, usually few in number and contain necrotic cellular elements; these are composed



Fig. 1. (*above*) Contact dermatitis (low power). Showing epidermic vesicles. A proved case of *Rhus* dermatitis.

Fig. 2. (*below*) Contact dermatitis (low power). Primary irritant type, showing superficial necrotic vesicle.

of cells of the cutis reaction, polymorphonuclear leukocytes and at times some of the epidermal cells (Fig. 2).

The vesicle in this group is frequently in the upper part of the epidermis, but may be anywhere; even in the cutis. In this event, the necrotic areas are often near the sweat ducts as they enter the rete pegs, or near the hair follicles. Many substances may be primary irritants and among these the heavy metals and the halogen group are frequent offenders.

Patch tests other than the tuberculin group show the same features as contact dermatitis. They show the two types of reaction and the same pathologic features (Fig. 3).

#### NEURODERMATITIS

Atopic dermatitis or disseminated neurodermatitis shows a chronic inflammatory process involving the small arteries rather than the capillaries. The epidermis while acanthotic always remains dry unless secondarily eczematized.

The vessels of the mid and upper corium are dilated and the walls thickened. There is some interstitial edema throughout the entire corium. About the vessels there is a moderate focal cellular infiltration of small round cells and wandering connective tissue cells. There are no leukocytes. The capillaries do not appear altered.

The epidermis is more or less regularly acanthotic, the rete pegs as well as the suprapapillary plates are involved. The basal cell margin is intact. Little or no edema of the epidermis is to be noted. The granular and horny layers are present throughout. In fact, often these zones are increased (Fig. 4). Parakeratosis is not present unless the eruption is eczematized. In other words, real scaling is never a clinical feature in this disease.

#### NUMMULAR ECZEMA

We believe that this disease belongs more to the neurodermatitis than the eczema group. Little has been written on the pathology of this disease. It is often clinically confounded with other dermatoses, as fungus infections, contact dermatitis, and even dermatitis herpetiformis.

The pathologic features of this disease appear to be chiefly those of neurodermatitis plus an epidermic vesicle. The cutis and epidermis are similar to neurodermatitis. In addition, there is the intraepidermic vesicle or vesicles about which there is little or no edema (similar to the contact vesicle).

The cutis reaction is that described under neurodermatitis. The epidermis is regularly acanthotic and in the upper portion one or sometimes several small vesicles are present. About these there is little or no evidence of edema. The vesicles contain chiefly fluid (Fig. 5), but may contain some cellular elements. These are predominantly polymorphonuclear leukocytes (Fig. 6).

#### ECZEMA

Here the cutis is primarily involved and the epidermis secondarily. Throughout the upper and mid cutis the vessels including the capillaries



Fig. 3. (above) Patch test-nickel sulfate (low power). Showing superficial necrosis.

Fig. 4. (below) Neurodermatitis (low power). Demonstrating regular acanthosis, no edema of the epidermis and a focal cellular reaction.



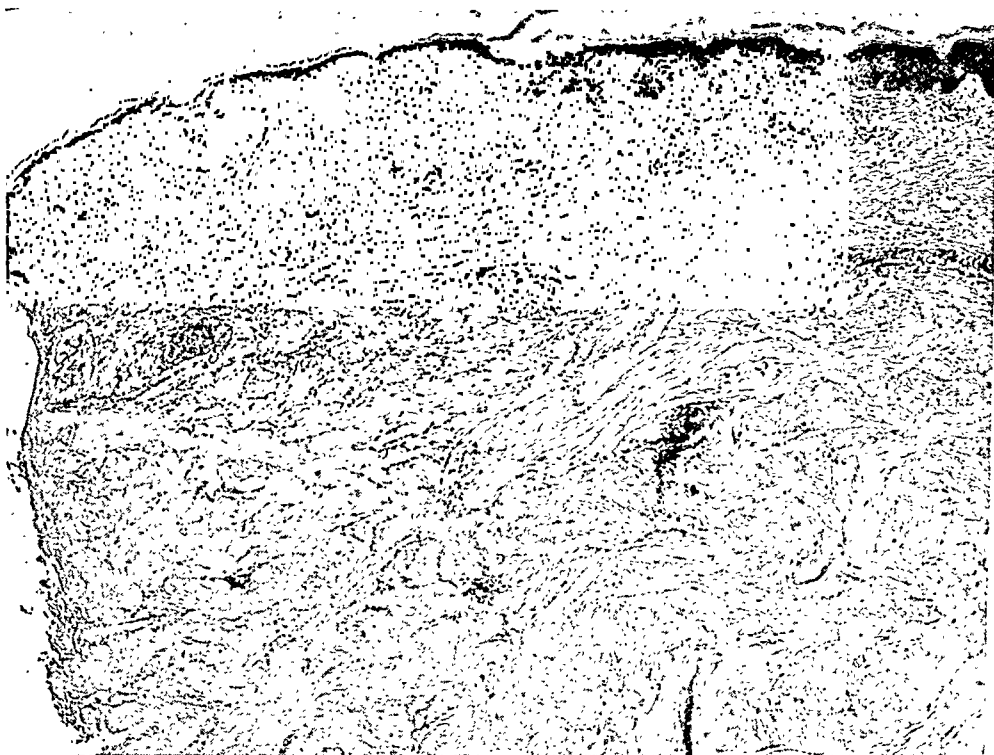


Fig. 5. (*above*) Nummular eczema (low power). Demonstrating epidermic vesicles with no edema about them; also a focal cellular reaction.

Fig. 6. (*below*) Nummular eczema (low power). Showing small area of necrosis rather than vesicle.

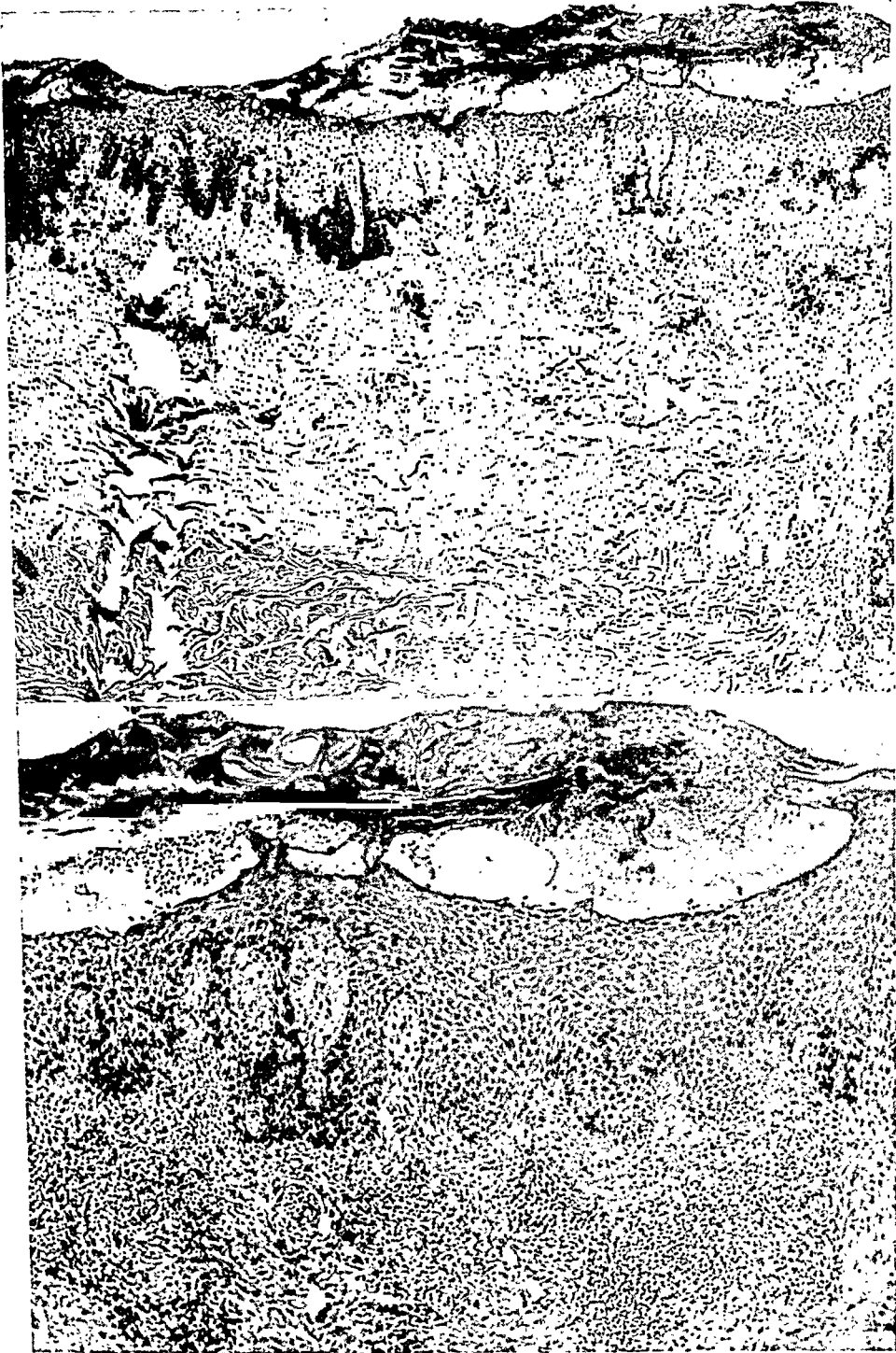


Fig. 7. (*above*) Chronic eczema—wet type (low power). Demonstrating irregular acanthosis; edema of the epidermis and a diffuse cellular reaction.

Fig. 8. (*below*) Chronic eczema—same as Fig. 7 (high power). Showing edema of the epidermis, intercellular edema, spongiosis and vesicle formation.

are dilated. There may be varying degrees of interstitial edema and a pronounced focal and diffuse simple type cellular infiltration. The papillary bodies are of all sizes and shapes (Fig. 7).

The epidermis is irregularly acanthotic; the rete pegs as well as the suprapapillary plates. There may be all the evidences of edema or just a few. At times pseudo rete pegs are formed. Parakeratosis is present but usually in small areas and in the intervening zones the granular layer is retained. When vesicles do develop the surrounding epidermis, even down to the basal cell zone, shows signs of edema (Fig. 8).

The pathologic features of infantile eczema and of seborrheic eczema differ in no way from the microscopic findings just described. In other words, these diagnoses are established by exclusion rather than upon specific findings. To diagnose these dermatoses, one must know the history and the clinic picture and then eliminate the other possibilities.

To a good measure the same statement holds true for the superficial fungus diseases. However, at times, with proper examination and staining, fungi may be demonstrated in the stratum corneum (Fig. 9).

When the edema of the epidermis subsides, the epidermis remains irregularly acanthotic; the granular and horny layer are present and at times increased. The cutis reaction is unchanged (Fig. 10). This is the picture referred to as lichenification. While clinically the findings closely resemble those of neurodermatitis, pathologically the differentiation can be made.

#### SUMMARY

1. Contact dermatitis differs from the other diseases by the type of vesicle, little or no acanthosis, and a mild superficial inflammatory reaction.
2. Neurodermatitis has a nonedematous regular acanthosis, thickening of the walls of the small arteries and a focal cellular reaction.
3. Nummular eczema has the epidermis and cutis of neurodermatitis, plus an intraepidermic vesicle.
4. Eczema is not a disease *sui generis* but probably an expression of several diseases having similar findings. It differs from the other three by an extensive cutis reaction involving the capillaries and intense diffuse cellular reaction. There is also an irregular acanthosis, most often with all signs of edema and sometimes with little or none.

#### DISCUSSION

In all four groups of disease the pathologic process is superficial. In none of these is degeneration found and the cellular reaction never contains plasma, epithelioid or giant cells. There is no evidence of sequelæ once the process subsides.

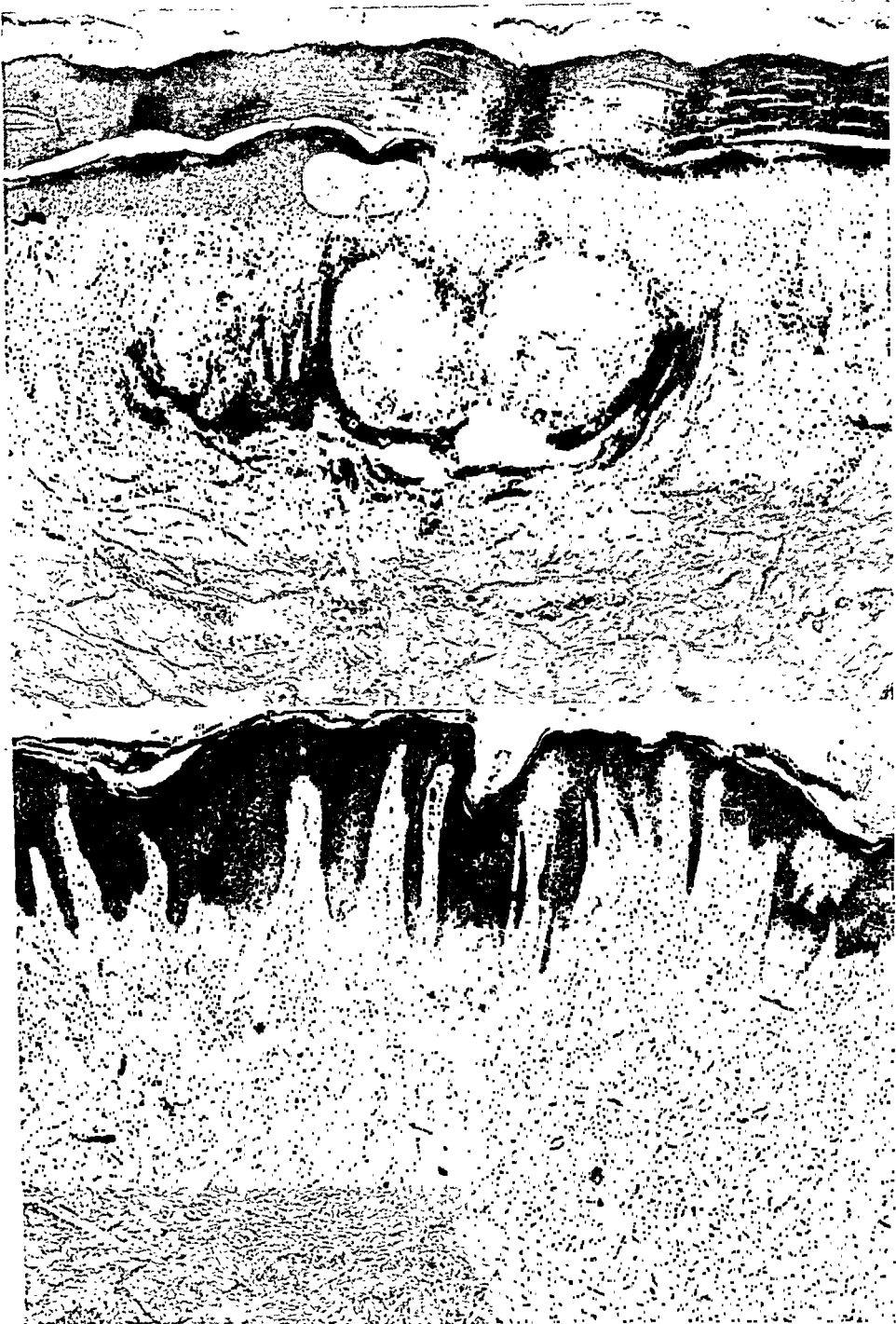


Fig. 9. (*above*) Dysidrosis (high power). Showing vesicle of dysidrosis. Organisms were demonstrated in the stratum corneum.

Fig. 10. (*below*) Chronic eczema—dry type (low power). Showing lichenification, irregular acanthosis, nonedematous epidermis and a focal and diffuse cellular reaction.

In contact dermatitis the epidermis plays the prominent role; in neurodermatitis the small arteries; in nummular eczema the same as neurodermatitis plus a peculiar epidermic vesicle; in eczema the cutis is the important feature, especially the involvement of the capillaries.

## CONCLUSION

The experimental work on these diseases has been chiefly clinical, dietary, blood, urine, etc. Of late years they have been studied especially by allergists or those interested in the field. It seems to us that much may be found by more intensive studies of the pathologic features. The diseases can be differentiated by this means and important clues may be discovered concerning the "shock tissue" involved and possible etiologic factors. We have hinted at the latter throughout this paper, but feel it premature to do more.

## CONCLUSIONES

El trabajo hecho sobre estas enfermedades ha sido principalmente clínico, dietético, químico (sangre, urina, etc.). Recientemente ellos han sido estudiados por los alergistas y aquellos interesados en este tema. Nos parece que mucho se puede descubrir por estudios más intensos sobre los puntos patológicos. Las enfermedades se pueden diferenciar por estos métodos, y se pueden descubrir puntos importantes concernientes al "organo de choque" envuelto, y posiblemente los factores etiologicos. Hemos aludido a éste último en todo el artículo, pero nos parece que todavía es prematuro hacer algo más.

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ALLERGY TO LIVER EXTRACT. Engelhardt, H. E., and Derbes, V. J.: South. M. J., 37:31, (Jan.) 1944.

Four cases are presented: three of which are characteristic of Tausk's classification of reactions to parenteral liver extract. The erythematous type is characterized by redness, local or general, following the first injection. Gradual tolerance is obtained with repeated injections. The histamine type is demonstrated by faintness, fall in blood pressure, and N. and V., which may occur at any time during course of therapy. Truly allergic reactions occur with a gradual development of sensitivity to a substance which was originally harmless. These reactions have been characterized by redness, heat, swelling and pain at the site of repeated injections. The fourth case demonstrated the presence of antibodies. This patient had severe general reaction which was characterized by weakness, difficulty in breathing, loss of consciousness, and a swollen tongue. The authors believe reactions to liver extracts are more common than the literature would suggest.

They recommended injections in the buttocks with patient lying down; alternating the site of the injection; changing the brands of the extract or attempting desensitization. The allergy present is to the liver itself and not to the animal. It is organ specific and not species specific. Bibliography.

L. J. H.

# PRECIPITATION OF PULMONARY EDEMA BY AN OVERDOSE OF ANTIGEN IN A PATIENT WITH RHEUMATIC MITRAL DISEASE

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THE subject of this report is observations on an allergic patient with rheumatic mitral heart disease in whom the administration of an overdose of pollen antigen precipitated acute pulmonary edema and cardiac decompensation.

## REPORT OF CASE

The patient, a white married housewife, thirty-seven years of age, was under treatment in my office for asthma and hay fever. She is a member of a highly allergic family. One sister has hay fever and her two children suffer from nasal and bronchial allergy.

She had suffered from severe seasonal asthma and hay fever for a period of eighteen years with complete freedom of symptoms outside the pollen seasons. On skin testing by the scratch-test method, she gave many positive reactions to the prevailing pollens of the San Francisco area. A suitable pollen antigen had been prepared and had given considerable relief to the patient. The patient's desensitization was progressing satisfactorily and without any undesirable reactions either local or systemic.

The patient was known to have suffered from rheumatic disease at the age of fifteen years and was known to have developed cardiac signs characteristic for rheumatic mitral heart disease in the form of a combined mitral stenosis and insufficiency. The x-ray findings of the patient's chest were consistent with this diagnosis. At the time referred to in this report, the patient showed good cardiac reserve and on careful questioning denied having experienced any of the symptoms or signs of cardiac decompensation.

In all other respects the patient's history was noncontributory. On May 6, 1941, she reported to the office for administration of a routine dose of pollen antigen. The interval between this injection and the previous one had been thirty-four days. The increase in dosage was 20 per cent of the dosage previously well tolerated and was taken from the same bottle of antigen. It is obvious that it was a mistake to increase the dosage after this interval; treatment should have been resumed with a smaller dosage or at most with the repetition of the same dosage. After the injection, the patient remained in the office for twenty minutes and after the local reaction at the site of injection had been found to be within the usual limits she started to return home. She walked briskly to reach a certain point in the city when she suddenly noticed that upon coughing a thin watery clear, not frothy, slightly pink fluid appeared. There was some respiratory distress very clearly recognized by the patient as different from her asthmatic attacks. The coughing became violent and she returned to the office in a taxicab.

On arrival at the office the patient presented the following condition: the skin was greyish and a little cyanotic, she was obviously in great distress mainly from incessant coughing and in obvious panic. She voluntarily assumed a sitting position leaning forward and supporting herself on her arms outstretched in front of herself. The respirations were 40 a minute, the patient seemed to cough in short quick coughs almost between every respiration and brought up an almost steady flow from nose and mouth of thin pink, nonfrothy, clear liquid, very similar to slightly bloody serum. During the time of observation the amount

of this discharge was nearly 200 c.c. The patient's blood pressure in millimeters of mercury was 80 systolic and 50 diastolic against her normal pressure of 104 and 58, respectively. Her pulse was in excess of 140 beats per minute. The site of the injection of the antigen showed a moderate local reaction about one inch in diameter. Examination of the lungs revealed many fine moist rales throughout without any of the signs characteristic for asthma. The patient repeated: "This is not asthma, something else must have happened to me." She spoke with the greatest difficulty. It was assumed that the patient was suffering from a delayed form of allergic shock.

Routine treatment was started. The office staff had been minutely trained and instructed for such an emergency: a blood pressure cuff was applied above the site of the injection, 0.3 c.c. epinephrine solution 1:1000 was injected through the skin puncture of the original injection of antigen, 1 c.c. of epinephrine was injected into the patient's leg subcutaneously and 1 c.c. of epinephrine in oil was injected into the muscles of the thigh. The only response from these measures was a perceptible increase in the patient's blood pressure which was not actually recorded. After approximately ten minutes, an intravenous infusion of aminophyllin 0.5 grams in 10 c.c. of solution was started. Twenty minutes after the patient arrived at the office, these measures had been carried out without any benefit to her. It appeared then that the patient's condition was not one of either a simple systemic reaction nor one of typical allergic or anaphylactic shock. A quarter grain of morphine was then administered and within another ten minutes the patient began to relax, and the cough and the discharge of fluid from the lung ceased. Within an hour from this time the patient had fallen asleep and slept lying flat on the couch for two hours. By five o'clock she insisted on returning to her home where she spent a satisfactory night. At the time the patient left the office her respiration was subjectively and objectively normal. She did not exhibit any other manifestations such as abdominal griping, diarrhea, involuntary bowel movement or urination, pounding in the head or ears, urticaria, itching of the palms or any of the coma-like prostration said to be characteristic of allergic shock.

A smear was obtained from the pulmonary secretion and was found to contain very few intact cells but an abundance of shadows of red cells within the clear coagulated serum.

Subsequent course: The patient continued treatment after one week's interval and has since tolerated all injections of pollen antigen without any unusual reaction and with great benefit to her pollinosis. She has received and tolerated dosages as much as ten times the doses which precipitated the events related above.

However, the patient's cardiac reserve has not returned to normal. During the week following the accident, she noticed that she became dyspneic on effort and that her pulse was faster than previously and that she tired more easily. She responded well to digitalis in the usual dosage and has been found to require a maintenance dose of 0.1 grams daily. She has not experienced any auricular fibrillation.

*Discussion.*—It is clear that this patient received an overdose of pollen antigen. However, her response to this overdose appears to be quite unusual. She did not exhibit what is usually referred to as a systemic reaction as a comparison of the events reported with any textbook description of such a systemic reaction will show. Neither did she suffer from shock or what Vaughan calls a "constitutional reaction," as is also clear from a comparison with the pattern of the reported nonfatal cases of

shock. It is remarkable that this patient did not recover as one might expect her to recover after either a systemic or a constitutional reaction. As a matter of fact, her lasting cardiac decompensation dates subjectively and objectively from the time of this accident.

I believe that the pathogenesis of this patient's experience may be interpreted as follows:

The condition of her heart was such that she was threatened with cardiac decompensation and any precipitating factor would have produced such decompensation. I believe that in this patient's case, the precipitating factor was the overdose of pollen antigen. It remains speculative as to which of the possible mechanisms may have precipitated the break in cardiac reserve or whether a combination of effects produced it.

1. There may have been a direct effect on the heart muscle; I am not familiar with any electrocardiographic studies during systemic or constitutional reactions which would support this assumption. No electrocardiographic studies were made of this patient at the time of the accident and electrocardiographs taken since do not, of course, contribute to the solution of this problem. I have planned to set up an office organization which will permit the taking of routine electrocardiographs in all future cases of general reactions, if they should occur.

2. The increased capillary permeability known to be a part of this type of reaction to an overdose of antigen may have made manifest the cardiac decompensation in a patient, who was already close to cardiac decompensation. I see no possibility to ascertain which of these mechanisms was operative in this patient with the information available. I have been unable to find in the literature a similar case. In relation to the precipitation of cardiac edema the reference of Vaughan's in his textbook on allergy is of interest. He writes: "I have seen true pulmonary edema occur in a decompensated cardiac, the attacks being initiated by exposure to inhalant and ingested allergens."

The therapeutic aspect of this problem is of significance; the administration of epinephrine was not sufficient. In simple systemic reactions with asthma and urticaria, epinephrine of course is adequate and sufficient treatment, and morphine would be contra-indicated. I believe that the administration of morphine in a case like the one reported is essential for recovery. A venesection might have been a logical measure to reduce the overload in the pulmonary circulation, and the administration of oxygen under pressure may have been beneficial with acute pulmonary edema.

#### SUMMARY

Cardiac decompensation occurred in a patient with rheumatic mitral disease as a result of an overdose of pollen antigen. The mechanism of this occurrence and the therapeutic implications are discussed.

It appears that this occurrence represents a special form of cardiovascular complication of a generalized reaction to an overdose of antigen in a cardiac patient.



It is believed that this type of response should be distinguished from both the systemic and constitutional types of reaction both on account of the underlying mechanism and the therapeutic implications.

## SUMARIO

Ha ocurrido una decompensación cardíaca en un enfermo con enfermedad mitral reumática por causa de una dosis excesiva de antígeno polénico. El mecanismo de esta ocurrencia y las implicaciones terapéuticas son discutidas. Parece que esta ocurrencia representa una forma especial de complicación cardiovascular de una reacción generalizada, debida a una dosis excesiva de antígeno en un enfermo cardíaco. Se cree que este tipo de respuesta debe ser distinguido o diferenciado de ambos tipos de reacciones, la sistémica y la constitucional, ambas por causa del existente mecanismo y las implicaciones terapéuticas.

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SCIENTIFIC BASIS FOR THE RECOMMENDED DIETARY ALLOWANCES. Roberts, Lydia J.: New York State J. Med., 44:59, (Jan.) 1944.

Dietary allowances have been formulated from a thorough study and appraisal of the literature and upon the judgment of clinical and research authorities in this field. Caloric requirements vary with the size and activity of the individual. The best guide for children is the amount the appetite demands, if growth is normal. Protein allowances for adults are based on the standard "one gram per kilogram," with higher allowances for pregnancy. In children, gradual decrease is provided from 4 gm. in infancy to adult allowance. The allowance for calcium intake has been tentatively set at 0.80 gm. for a 70 Kg. man, a figure above the widely used 0.67 gm. of the Sherman standard. Allowance of 1 gm. has been provided in children. Phosphorous intake, for which no standards were set, is assured by foods providing calcium. Adult iron allowance is the accepted 12 mg. standard, with an increase of 3 mg. for pregnancy. Childhood iron allowances range from 0.5 mg. as minimal in infancy to 0.4 mg. in preschool children. Vitamin requirements have shown great divergence in the judgment of authorities. The allowance of 5,000 I. U. of vitamin A for adults is established. Requirement is based on body weight rather than energy expenditure. Hence requirements for children range from 550 I. U. at one year to 3,330 I. U. at sixteen years. Adult and child allowances of thiamine are based at 0.5 mg. per 1,000 calories. Riboflavin allowances are derived by increasing the thiamine basis by 50 per cent. Nicotinic acid requirements are given as ten times the thiamine allowances. Ascorbic acid allowances range from 75 mg. for adults to 30 mg. in infancy. Allowances for vitamin D in adults may be obtained adequately from nondietary sources. Minimal amounts of 400 to 800 I. U. are recommended for infants, in pregnancies and adults unable to obtain adequate intake from other sources.

L.J.H.

## PSYCHIATRIC STUDIES IN CLINICAL ALLERGY

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THE present paper which is concerned with the psychiatric components of the allergic personality marks the extension of work in progress on the personality variables encountered in the asthmatic syndromes. The previous contributions dealt with the nature of the clinical manifestations of the condition and emphasized, in detail, the specific trend of this type of functioning personality<sup>1</sup>: the directions in which abnormalities, when present, were to be sought; and surveyed the pertinent literature<sup>4</sup>. The present paper stresses the specific *purposeness* of the disease to particular patients and dwells largely on the nature of the sufferer himself. Based on the study of the personality variables of forty asthmatic patients and forty allergic (non-asthmatic) patients with twenty normal individuals for experimental control, the same personality variables were looked for in a group of patients judged as mentally abnormal. To indicate the progress and technique which made these further studies possible, the essential emergents of the previous papers are briefly recapitulated.

### PERSONALITY APPRAISAL

In the earlier studies, the personality "make-up" was first assessed in terms of the normal psychological components adjudged on normal criteria. By employing the technique epitomized in Table I as a frame of reference, the forty patients suffering from bronchial asthma of an allergic type were found to arrange themselves according to the pattern of distribution seen in Chart 1. The findings for the allergic nonasthmatic subjects and the normal control patients were also obtained. It can be seen that the allergic asthmatic group differs from the allergic nonasthmatic, both being distinctly different from the nonallergic normal controls. The significant aspect of these findings are the subject of comment and discussion in the original survey.<sup>5</sup>

For the present paper, the abnormal aspects of personality were tested for by an independent technique. The neurotic elements of deviation being determined separately by a psychiatric assessment of the patient and his background, gave us a score which indicated the degree of severity of the attendant neuroses. When tested by such criteria, as summarized in Table II, twenty of the patients in the series were considered to be, in every way, normal. Seventeen showed character anomalies and of these, eight presented significant neurotic manifestations. These form a subject of special import to the comprehension of the allergic reaction mode. It

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TABLE I. PERSONALITY VARIABLES ENCOUNTERED IN ALLERGY

ABILITY Administrative Sensitive Imaginative Executive Inventive	HABITUS Pyknic Dysplastic Leptosomatic Athletic Asthenic	INSTINCT Assertive Aggressive Autistic Associative Abstractive	INTERESTS Persons Relations Objects Events Ideas	MANNER Imposing Serious Complacent Deliberate Intelligent
ATTITUDE Open-minded Tortuous Valved Superficial Cryptic				METHODOLOGY Clean-cut Hide-bound Slipshod Orderly Categoric
CHARACTER Expansive Retractive Fluent Reflexive Suspicious				MOOD Euphoric Intense Vacillating Shallow Imperturbable
CONSTITUTION Phasic Regulative Impulsive Reactive Progressive				NEUROSIS Elative Depressive Regressive Conversive Hypochondriac
EMOTIONALITY Extremes Moody Stable Excitable Impervious				ORGANIZATION Cycloid Repetoid Schizoid Hysteroid Paranoid
EXPERIENCE Organized Involved Subjective Creative Theoretic				TEMPERAMENT Explosive Surgent Idealistic Ebullient Provocative
FUNCTION Sensitive Affective Intuitive Conative Cognitive	TREND Optimistic Urgent Fluent Audacious Casuistic	TYPUS Dynamic Empathic Detached Animated Essential	TRAIT Ambitious Rigid Persistent Responsive Querulous	WILL Exploitive Tyrannical Individual Submissive Didactic

should be noted that in our previous studies, using the same scale of inquiry, 25 per cent of our asthmatic subjects showed a marked degree of neuroticism.

TABLE II. A SCALE OF NEUROTICISM

- 1 One or both parents or siblings are understood to present neurotic disturbances.
- 2 There has been a definite parent-child conflict situation.
- 3 The patient, as a child, was subject to "nervousness" or to problem behavior.
- 4 There was present, before onset of asthma, a marked character-trend.
- 5 The illness was caused by emotional trauma.
- 6 A psychologic precipitant (overt or manifest) is responsible for the majority of the attacks.
- 7 The subject is exploiting his paroxysms for psychological ends.
- 8 There is a well-defined character warping as a result of the attacks.
- 9 There are current matrimonial or domestic conflicts present.
- 10 The present personality shows signs of neurotic disability.

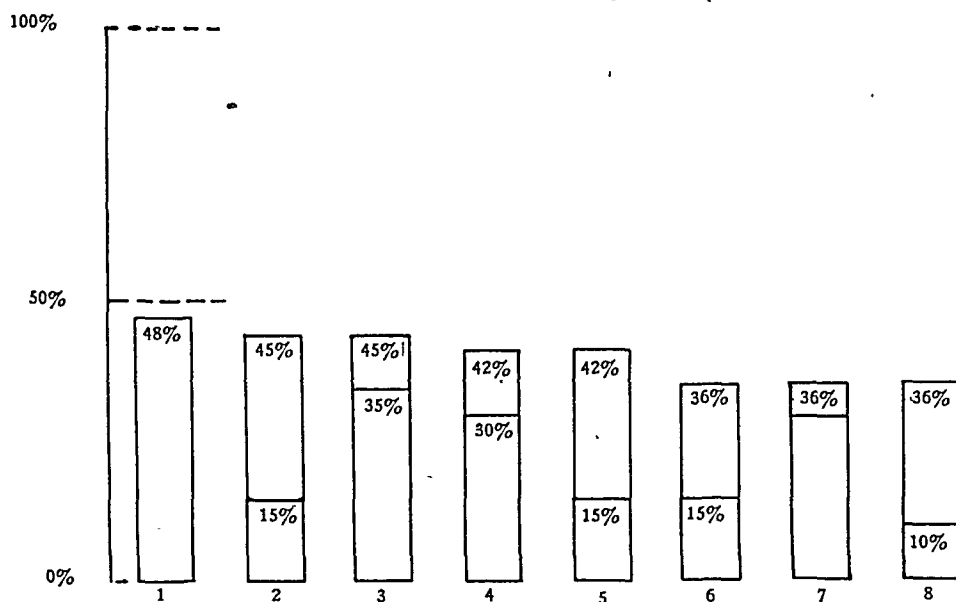
Total

## CODE OF CLASSIFICATION

In a previous paper<sup>5</sup>, the patients were classified in type as labeled with the letters A to E inclusive. The remaining tables of the present paper can best be understood by referring to Table IV, in which it may be seen that the patients are classified under five headings, labeled alphabetically. To take one type as an example, the letter A, when referring to culture, represents American, and, when referring to facies, represents the Pyknosome type. It is not necessarily true that all the other characteristics labeled A

# CLINICAL ALLERGY—BROWN AND GOITEIN

CHART 1. PERSONALITY VARIABLES PECULIAR TO THE ASTHMATIC POPULATION (UPPER BLOCKS) AS COMPARED WITH NORMAL CONTROL SUBJECTS (LOWER BLOCKS)



Key: (1) Personality as Cycloid and Paranoid; (2) Function as Conative; (3) Mood as Poised; (4) Habitus as Pyknic; (5) Character as Constrained; (6) Biotype as Reactive; (7) Disposition as Ascending; (8) Maladjustment as Obsession and Conversion.

TABLE III. CODE OF CLASSIFICATIONS

Code Letter	A	B	C	D	E
Culture	American	Scandinavian	Irish	Latin	Slavic
Facies	Pyknosome	Dysplastic	Leptosome	Athleticsome	Asthenic
Character	Expansive	Constrained	Fluent	Responsive	Abstract
Mental Biotype	Phasic	Regulative	Impulsive	Reactive	Progressive
Mental Function	Sensating	Affective	Intuitive	Conative	Cognitive
Mental Constitution	Bluff	Urgent	Resilient	Audacious	Astute
Mental Attitude	Open (minded)	Tortuous	Recoiling	Superficial	Cryptic
Mental Disposition: Dominant	Ascendancy	Precision	Autonomy	Vivacity	Curiosity
"Recessive"	Rage	Hate	Spontaneity	Ardor	Revolt
Temperament	Explosive	Surgent	Idealistic	Ebullient	Contentious
Mood	Exalted	Intensive	Vacillating	Flighty	Poised
Personality Organiza- tion (Behavioral)	Dynamic	Emphatic	Detached	Animate	Essential
Personality (Clinical)	Cycloid	Repetoid	Schizoid	Hysteroid	Hypochondroid
Maladjustment	Euphoria	Obsession	Regression	Conversion	Hypochondria

are specifically American. This classification permits us to list seventy qualities by five letters, making it possible to present a personality profile for any patient in a very succinct manner. To look ahead for an example,

# CLINICAL ALLERGY—BROWN AND GOITEIN

TABLE IV. PATTERN OF DISTRIBUTION OF PERSONALITY VARIABLES IN ALLERGY SUBJECTS  
(All in Percentage)

	40 Asthma Subjects					40 Allergic Subjects					20 Normal Controls				
	Type A	B	C	D	E	A	B	C	D	E	A	B	C	D	E
Habitus	42 Pyknic	6	10	6	36	40	4	20	12	12	30	5	25	25	15
Character	22 Expansive	42	6	18	12	25	30	5	30	10	25	15	20	10	20
Personality Organization	24 Cycloid	22	12	18	24	20	30	5	30	15	25	5	25	15	30
Mental Function	10 Sensating	30	5	45	10	15	30	0	45	10	40	5	5	15	35
Mental Attitude	45 Open-minded	20	5	15	15	30	15	15	25	15	45	25	10	0	20
Disposition Dominant	36 Ascendancy	24	16	12	12	10	15	25	45	5	30	10	15	20	25
Recessive	16 Rage	32	12	8	32	10	30	5	45	10	30	10	15	20	25
Temperament	22 Explosive	18	15	30	15	10	25	5	35	25	25	5	15	30	25
Mood	15 Exalted	25	5	10	45	10	25	5	20	40	0	30	0	35	35
Mental Biotype	18 Phasic	30	6	36	10	10	25	10	40	15	40	5	10	15	30
Maladjustment	2 Euphoria	13	5	13	10	0	15	2	25	0	0	0	0	10	0
		(57% Normal)				(58% Normal)					(90% Normal)				

## DEFINITIONS OF TERMS AS USED IN PRESENT DISCUSSION

*Character.*—The sum-total of socially manifesting trait constellations and enduring tendencies, as the result of habit development.

*Mental Biotype.*—The major psychic disposition, innate or acquired, influencing (and manifest in) a person's behavior, expressed in its instinctual aspect.

*Function.*—The dominant mode of apperception and conception in the individual; his secondary function in a Jungian sense.

*Constitution.*—The manifest quality of mental constellations result of social trends and drives.

*Attitude.*—The habitual "frame of mind" characteristic of the individual; his mode or responsiveness and degree of accessibility, his "set" toward phenomena.

*Disposition-Dominant.*—The instinctual tendency and drive most evident in social behavior; the constellation in his psychic nature most representative of the man.

*Recessive.*—The latent or suppressed instinctual trend inferred from (or revived at) interview.

*Temperament.*—The presence of a permanent organization in the individual of a psychosomatic feeling tone in response to inner and outer organic conditioning. "The sum of effects, upon the mental life, of the metabolism or other chemical changes constantly going on in the human body" (McDougall).

*Mood.*—The more transitory manifestation of emotional attitudes, and the awareness of a disturbed psychosomatic equilibrium.

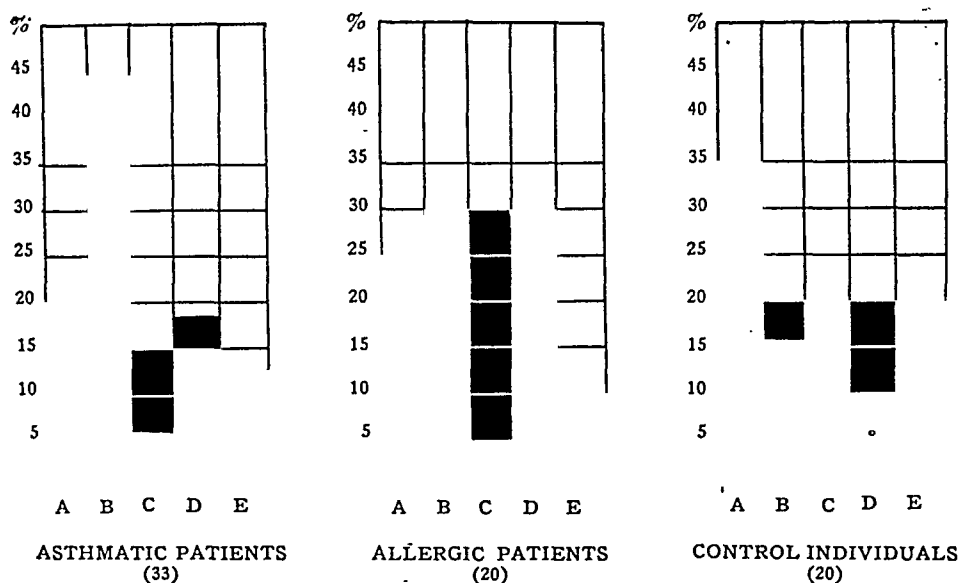
*Organization.*—The psychic responsiveness and "set" of the organism as a whole, expressed in clinical terms.

*Maladjustment.*—The manifest expression of psychiatric abnormality, with tendencies denoting departures from clinical norm in the direction indicated.

Case 1, Table III, is Slavic in culture, athleticsome in facies, responsive in character, reactive in bio-type, affective in function, tortuous in mental attitude, and shows curiosity as an instinctual dominant, and hate as a mental recessive. He is surgent in temperament, poised in mood, while his clinical personality is repetoid in type, his maladjustment an anorexia nervosa. It is hoped that by this example the reader, unaccustomed to the use of tables of this sort, will be able to analyze the material in Tables V to XIII, working out the personality profile for each of the patients.

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## CHART 2. CHARACTER-TENDENCY



Reference to Table III under the heading, Character, lists A as Expansive; B as Constrained; C as Fluent; D as Responsive; E as Abstract.

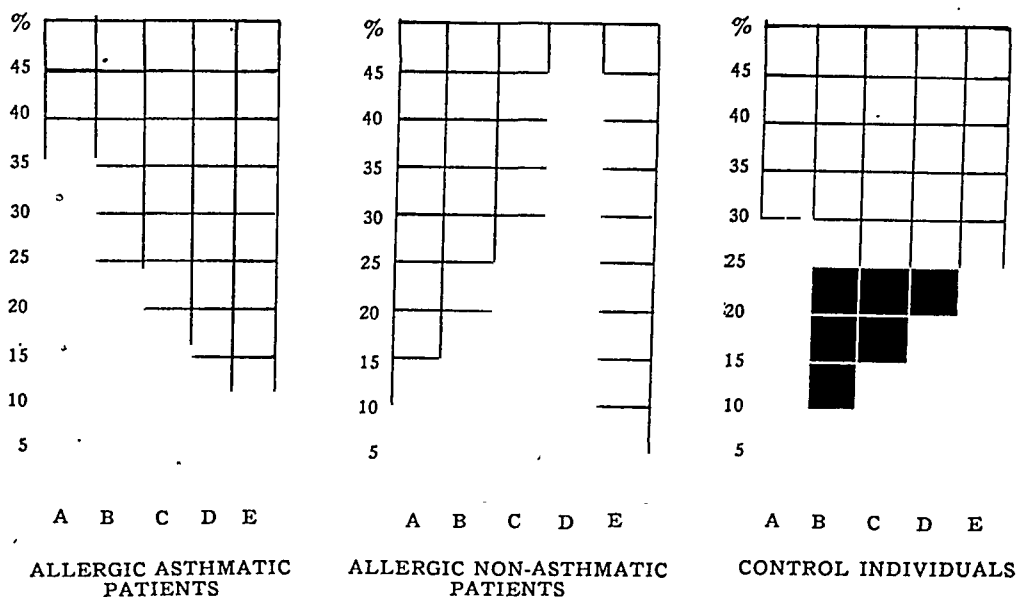
### THE ASTHMA COMPOSITE PERSONALITY

It would seem (Table IV) that the outstanding type of personality involved in bronchial asthma, as deduced from the findings of the total population, is a person with a pykno-somatic habitus, expansive in character, open-minded in attitude and phasic in his mental bio-type. He is a practical extrovert with ascendance (pride and satisfaction) as his dispositional Dominant, with suppressed rage as a recessive feature. He is ebullient and sanguine in his temperament; "poised" in his moves and clinically, in his personal organization, a blend of the dynamic and the essential, tending to be cycloid and hypochondroid in type. He is somewhat prone to neurotic maladjustment either of the excessive or hypochondriacal form. Such a patterning may well correspond to a definite "respiratory personality" (Sigaud), its subvarieties being determined by accentuation of the intake-hold or release aspects as in all oral types (Alexander).

Contradictory as it may seem, it should be noted that least frequently seen is that composite found in the lepto-somatic individual who is impulsive in bio-type and fluent in character, intuitive in function, recoiling in attitude, autonomous (and the least spontaneous) in disposition, idealistic in temperament, vacillating in mood and of a regressive tendency in neurotic maladjustment. All of these traits correspond to those met with in the schizoid personality. Our observations are, thus, in agreement with Nickum who notes the rarity of association of dementia praecox (under general personality make-up) with bronchial asthma.

The character tendencies of these patients when separated from the qualities can be shown in profile form. In Chart 2 it will be seen that a

CHART 3. MENTAL DISPOSITION



Reference to Table III, under the heading, Mental Disposition, lists A as Ascendancy; B as Precision; C as Autonomy; D as Vivacity; E as Curiosity.

character dominance of "retractive" traits such as neatness, exactness, and "stinginess" mark the asthmatic group as does an element of responsiveness (trigger action) higher than that seen among the control individuals who lean toward expansive traits of the type seen in optimism, grandeur and greed. There are developmental reasons for these differences.

#### THE MENTAL DISPOSITION OF ALLERGIC PATIENTS

When we attempt to contrast the allergic groups, (asthmatic or non-asthmatic, and containing both normal and neurotic patients) with the control population, as a whole, the specificity of the variables is not well marked. It is seen, however, that the disposition heads in certain directions and that unusually low readings, as for example in the field of curiosity, are again noteworthy for their relative absence; that is, there is a suppression of what is usually considered an instinctual trend. The degree of oral ascendancy is high in asthma while vivacity of disposition is high among the nonasthmatic patients, much higher than could be attributed to chance. These personality factors are of significance in indicating the types prone to the allergic reaction in particular and why success or lack of success in therapy may be bound up with the type of personality with which the physician is dealing. Other workers have pointed out the close alliance of certain dispositions with the reaction chosen. It can be seen from these studies that there are formative characterological factors, common, at once, both to the patient's disposition and his allergy. The profiles in Chart 3 delineating the mental disposition in allergic asthmatics and nonasthmatic allergic patients in terms of ascendancy, precision, auton-

# CLINICAL ALLERGY—BROWN AND GOITEIN

TABLE V. NEUROSIS AND PERSONALITY VARIABLES OF THE NEUROTIC GROUP OF (NON-ASTHMATIC) ALLERGIC PATIENTS

Case Number	Culture	Facies	Age	Character	Biotype	Function	Attitude	Instinctual Dominant	Recessive	Temperament	Mood	Personality	Neurosis
1	E	D	22	D	D	B	B	D	B	B	D	B	Anorexia Nervosa
14	A	A	50	D	D	D	D	D	D	D	D	D	Conversion Hysteria
21	C	C	25	D	D	D	D	D	D	D	D	B	Anxiety Hysteria
28	E	A	42	D	D	D	A	A	D	D	B	D	Compulsion Neurosis
37	A	E	32	E	D	D	D	E	E	E	C	D	Anxiety Hysteria
39	C	E	32	E	B	D	D	D	D	B	B	D	Obsessional Neurosis
40	E	D	23	B	D	B	D	D	D	B	D	B	Conversion Hysteria

(The letters A-E, inclusive, refer to Qualities listed in Table III.)

TABLE VI. MALADJUSTMENT AND PERSONALITY VARIABLES OF THE MALADJUSTED GROUP OF (NON-ASTHMATIC) ALLERGIC PATIENTS

Case Number	Culture	Facies	Age	Character	Biotype	Function	Attitude	Instinctual Dominant	Recessive	Temperament	Mood	Personality	Neurosis
3	A	D	25	B	D	D	D	D	D	B	B	D	Conversion Anxiety
5	C	E	24	B	B	B	D	C	B	C	B	B	Obsessional Reaction
10	C	E	25	B	B	D	B	B	B	B	B	B	Anxiety Reaction
16	E	A	47	B	B	D	D	D	D	E	E	B	Hysterical Anxiety
22	E	D	32	A	D	D	E	D	D	D	D	D	Emotional Instability
31	E	E	22	B	D	D	D	D	B	B	D	D	Obsessive Reaction
33	C	C	32	D	D	D	D	D	D	B	D	D	Hysterical Anxiety
34	D	E	41	B	D	B	B	D	B	B	D	B	Obsessive Reaction
43	B	A	38	B	B	D	A	B	E	D	A	B	Obsessive Reaction

(The letters A-E, inclusive, refer to Qualities listed in Table III.)

omy, vivacity, and curiosity show that the asthmatic nonallergic and the allergic nonasthmatic groups tend to be more precise or perfectionist but less curious in disposition as compared with the control individuals. The asthmatic subject, however, has greater innate ascendancy or masterfulness in his personality make-up while the allergic individual shows greater vivacity as the distinguishing mark of his personality.

## NEUROSSES AND MALADJUSTMENTS SEEN IN ALLERGIC PATIENTS

In those in whom the reaction tendency has not reached psychoneurotic proportions, it is necessary to distinguish between neurosis proper and personal maladjustment. Both were determined for our series of patients



## CLINICAL ALLERGY—BROWN AND GOITEIN

TABLE VII. THE NATURE OF THE NEUROSIS AND ITS RELATION TO THE PERSONALITY VARIABLES AMONG THE NEUROTIC GROUP OF ASTHMATIC PATIENTS

Case Number	Culture	Facies	Age	Character	Biotype	Function	Attitude	Instinctual Dominant	Recessive	Temperament	Mood	Personality	Diagnosis
2	C	A	35	B	B	B	A	D	A	B	B	A	Obsessional Neurosis
6	D	E	30	B	B	E	E	B	D	E	E	B	Schizoid Regression
12	E	D	25	B	C	E	C	C	E	C	E	C	Conversion Hysteria
15	C	E	25	E	A	C	A	E	E	B	B	E	Obsessional Neurosis
18	E	E	29	E	C	D	B	B	E	E	E	B	Hypochondriasis
19	E	E	60	B	A	D	E	E	B	D	A	E	Hypochondriasis
24	D	B	36	E	E	C	E	C	E	C	A	E	Paranoid
31	E	D	19	C	C	C	C	D	D	C	A	C	Schizoid Regression

(The letters A-E, inclusive, refer to Qualities listed in Table III.)

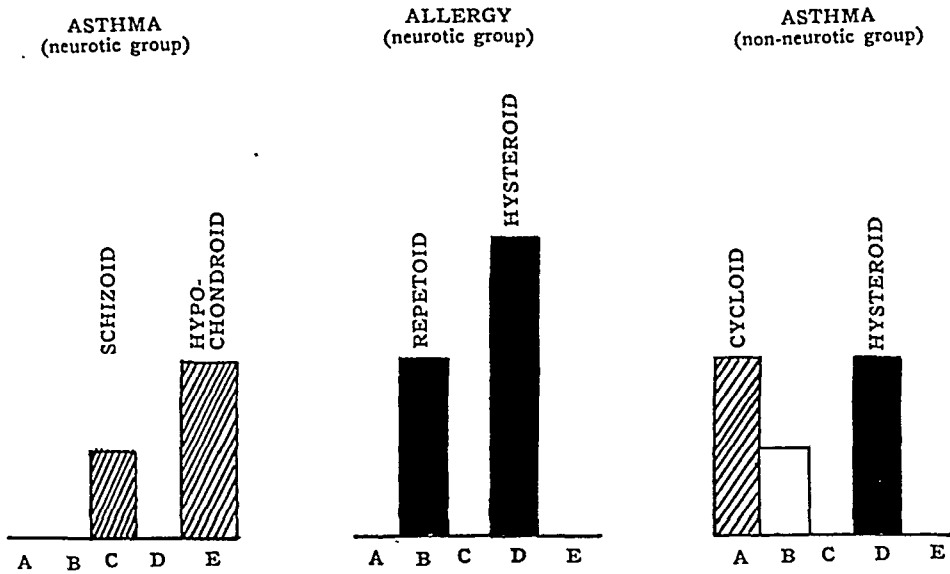
TABLE VIII. THE NATURE OF MALADJUSTMENT AND THE PERSONALITY VARIABLES AMONG THE EMOTIONALLY MALADJUSTED GROUP OF ASTHMATIC PATIENTS

Case Number	Culture	Facies	Age	Character	Biotype	Function	Attitude	Instinctual Dominant	Recessive	Temperament	Mood	Personality	Diagnosis
9	E	A	50	B	B	B	B	B	B	E	B	B	Normal with Obsessive Tendency
11	E	E	62	B	E	E	B	B	E	E	B	E	Hypochondriac Reaction
14	E	A	50	B	A	D	A	E	E	A	E	A	Hypomanic Reaction
16	C	E	30	D	D	D	A	A	E	D	A	D	Hysterical Reaction
22	C	E	20	B	B	B	C	C	B	C	E	B	Obsessional Reaction
26	A	D	12	D	D	D	A	D	D	D	D	B	Obsessional Reaction
27	C	E	16	D	D	D	D	D	D	D	E	D	Hysterical Conversion
30	A	A	11	D	C	D	C	C	C	D	C	C	Hysterical Trends
36	E	C	8	E	C	D	C	C	C	D	C	D	Hysterical Anxiety

by suitable psychiatric interviews and observations. Of the forty subjects, seven gave clear indications of neurotic disturbances ranging from obsessional states to conversion hysteria. It was noteworthy how certain personality variables typified the neurotic characters in question. The neuroses and personality variables of the neurotic group of nonasthmatic patients are listed in Table V as are the maladjustment and personality variables of the maladjusted group of nonasthmatic allergy patients listed

# CLINICAL ALLERGY—BROWN AND GOITEIN

CHART 4. PERSONALITY ORGANIZATION



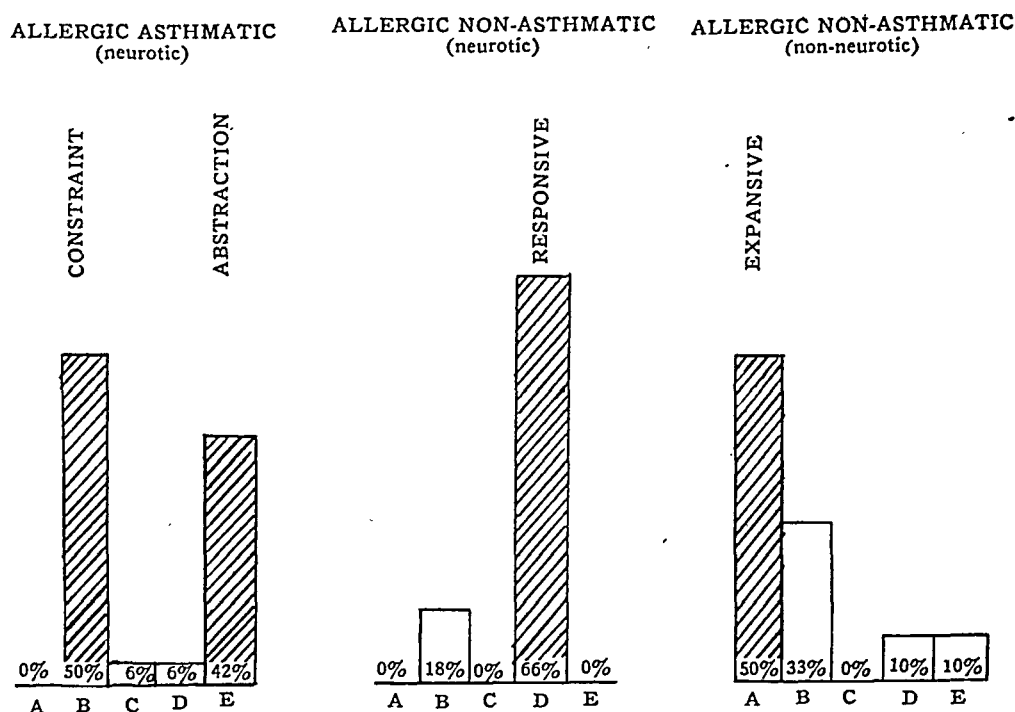
in Table VI. Considering the high incidence of allergic disease among the general population, it is evident that neurosis as either cause or effect must play a considerable part. The life histories of these patients make abundantly clear the reason for the sequence of events. It must be admitted that when character types are in evidence they sufficiently differentiate those prone to and those immune from the allergic reaction mode.

In Table VII is shown the nature of the neuroses and their relation to the personality variables among the neurotic group of asthmatic patients and in Table VIII the nature of maladjustment and the personality variables among the emotionally maladjusted groups of asthmatic patients.

When the asthmatic population is divided into neurotic and free groups, it will be noticed from Chart 4 that the pattern of personality and of character differs for the two groups as it does also between the asthmatic patients and the other patients, otherwise allergic. It will be noted from Chart 4 how the hypochondroid and schizoid tendencies mark the clinical personality of the asthmatic patients while the hysteroid and repetoid tendencies are seen in the patient who is otherwise allergic but not asthmatic.

It is equally clear from Chart 5 that there are constraint features such as niggardliness along with hypochondriacal preoccupations of an abstract type (considered as forerunners of obsessionism in the neurotic group suffering from bronchial asthma). There is a character trend predominantly of the responsive or hysteroid type in the neurotic group who are allergic but nonasthmatic. In these, the resulting neurosis is largely of the conversion and anxiety-hysteria type.

CHART 5. CHARACTER TENDENCY AMONG NEUROTIC AND FREE GROUPS



## CONCLUSIONS

The previous papers of this series presenting a cross-section of the asthmatic personality when viewing it as a dynamic pattern of behavior, demonstrated there was a special type of personality prone to asthmatic attacks. A sample population of asthmatic subjects and an equal number of nonasthmatic allergic subjects were classified for normal personality variables and tabulated under certain agreed headings previously defined. Each showed a specific pattern.

The asthmatic patient had a somewhat greater tendency than the normal to be left-handed, to marry, and was subject to emotional instability when compared either with other allergic patients or with the normal population of the same age and social group. There was no obvious correlation with color blindness, degenerative stigmata or twin inheritance. All the patients seem to be of average intelligence; but in 43 per cent the personality as a whole deviated from the normal and showed trends constituting abnormal or psychiatric personalities either in character anomalies or frank neuroses (20 per cent).

Psychiatric inquiries differentiated an abnormal personality of a special stamp (obsessive and paranoid). Neurotic and emotional maladjustment was discernable in 43 per cent of the asthmatic subjects as compared with 10 per cent in the control patients and 47 per cent in the allergic nonasthmatic subjects. Current neuroses were diagnosed in 20 per cent of the patients in two cases reaching a morbid degree, although no outstanding

phobia was encountered. The neuroses in allergic nonasthmatic patients totalled 16 per cent. It was considered as absent among the control subjects. These neuroses took the form of hypochondriasis, obsessionism, conversion and anxiety-hysteria; and (among the allergic nonasthmatic patients) vague anxiety symptoms, depression, obsessionism and hysteria. In both groups, the emotionally stable section admitted to a feeling of improvement as a result of physical treatment and seemed less inclined to mental resistance and obstinacy. They lacked the sense of dissatisfaction which was noted in the unstable section. The hysteroid type was more evident in the allergic neurotic patients and the obsessive type among the asthmatic neurotic patients. Diagrams illustrating the patterns of behavior are given.

#### CONCLUSIONES

Los artículos previos de esta serie presentando una sección transversal de la personalidad asmática, examinada desde el punto de vista de un modelo, ejemplo dinámico, ha demostrado que había un tipo especial de personalidad, dispuesto a ataques asmáticos. Un ejemplo de una población de sujetos asmáticos y una cantidad igual de sujetos alérgicos no-asmáticos fueron clasificados por variables de personalidad normal y tabulados bajo títulos ya aceptados y anteriormente descritos. Cada uno de ellos demostraron un modo específico.

El enfermo asmático tenía una tendencia algo más grande que la normal, a ser dejado, a casarse, y era sujeto a una inestabilidad emocional cuando se lo comparaba con los otros o con la población normal de un grupo social de la misma edad. No había ninguna correlación evidente con ceguera de color, estigmata degenerativa o herencia gemela. Todos los enfermos parecen sur de una inteligencia media, pero en 43% la personalidad en general, se había desviado de la normal y mostró tendencias constituyendo personalidades psíquicas o anomalías de carácter o verdaderas neurosis (20%).

Interrogaciones psiquiátricas diferenciaron una personalidad anormal de una clase especial (obsesiva y paranoidea. Un mal ajustamiento neurótico y emocional era perceptible en 43% de los sujetos asmáticos en comparación con 10% de los enfermos controlados y 47% en los sujetos alérgicos no-asmáticos. Las neurosis corrientes fueron diagnosticadas en 20% de los enfermos, alcanzando en dos casos un grado mórbido, aun que fobia notable no fué encontrada. Las neurosis en los enfermos alérgicos no-asmáticos llegaron a un total de 16%. Ellas fueron consideradas como ausentes en los sujetos que estaban bajo observación. Esta relación fué extremadamente significativa. Estas neurosis tomaron la forma de hipocondriasis, obsesionalismo, conversion y ansiedad-histerica; y (entre los enfermos alérgicos no-asmáticos) síntomas vagos de ansiedad, depresión, obsesionalismo e histéria.

En ambos grupos, la sección emocionalmente estable, admitió haber sen-

tido una mejoría por causa de un tratamiento físico y pareció menos inclinada a una resistencia mental y obstinación. Ellos carecieron del sentido de descontento que fué observado en la sección instable. El tipo histeróido fué más claro en los enfermos alérgicos neuróticos y el tipo obsesivo entre los enfermos asmáticos neuróticos. Se han presentado diagramas ilustrando las normas de conducta.

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CUTANEOUS TESTS WITH HEN'S EGGWHITE FRACTIONS IN ATOPIC INFANTILE ECZEMA. Ditzkowsky, S. E., Hecht, R., Cole, A. G., and Levin, B.: *Arch. Dermatol. & Syph.*, 48:258, (Sept.) 1943.

Unpublished experiments performed by one of the authors (R.H.) some years ago showed that patients who gave cutaneous reactions to tests with eggwhite might react to one or more of the various fractions (ovalbumin, ovomucin, ovomucoid and conalbumin) but that ovomucoid elicited by far the greatest number of reactions, there being few, if any, persons sensitive to eggwhite who were not sensitive to this component. Sensitization to eggwhite, if it occurs via the placenta, would probably depend in great part on a noncoagulable fraction (ovomucoid), since coagulated eggwhite would lose its characteristics during the process of digestion and would not reach the placenta in a form capable of stimulating immunological processes. The uncoagulable fraction could, however, reach the placenta and be passed over to the infant. The correctness of this theory might be proven by cutaneous tests on atopic children with the different fractions of eggwhite. Forty-six infants, half of whom were under one year of age, with typical atopic dermatitis were tested with eggwhite fractions and, incidentally, to chicken feathers. There were forty-one positive reactions to ovomucoid, forty to dried eggwhite, forty to fresh eggwhite, twenty-two to ovalbumin, seventeen to chicken feathers, fifteen to conalbumin, and nine to ovomucin. These experiments would tend to bear out the thesis (since both dried and fresh eggwhite contain ovomucoid) that since ovomucoid is the most resistant of the eggwhite fractions one might expect it to be responsible for and it is in fact the cause of the greatest number of positive reactions to cutaneous tests with eggwhite in infants and young children with atopic dermatitis. These observations also confirm the clinical fact that sensitization to eggwhite does not necessarily carry with it sensitization to chicken feathers or serum (conalbumin). It is also interesting in the above series that only six patients giving positive reactions to eggwhite were clinically sensitive to eggwhite. The others could be exposed to it without apparent harm.

J. G.

## POLLINATION OF ANEMOPHILOUS TREES IN NEW ORLEANS

WM. T. PENFOUND, Ph.D.

New Orleans, Louisiana

IN his book on allergy Vaughan<sup>5</sup> stated, "Each allergist in the United States has found that in order to obtain best results he must first have a very complete botanical survey made of his section of the country, to learn the botanical flora. He then tests his patients with the pollen of those plants which are indigenous to his section." At the present time the necessity for local plant and pollen surveys is recognized by all competent allergists, especially since it has been shown that the distribution of pollen allergens is often so specific that certain areas can be designated as ragweed, sagebrush, or mountain cedar regions.

A considerable body of data on the distribution of plant allergens has been compiled from botany manuals and with the help of local botanists. It is probable, however, that less satisfactory data are available on the blooming dates of anemophilous plants, since these require continuing observations on the part of local botanists and allergists over a period of several years. The ideal survey would include, not only the anthoperiods of the suspected plant allergens, but also a concurrent pollen analysis. This has been done but rarely in the history of investigations in allergy.

Vaughan<sup>5</sup> includes a total of fifteen tables giving pollinating dates of anemophilous plants. In some of these surveys only the generalized common names (e.g., elm, ash, oak) are given, leaving the reader at a loss to know to which species the authors refer. In other surveys only one specific blooming date is given for each species, leaving the reader to ponder whether this refers to the first individual of a species to bloom, the average date at which a given species begins to blossom, or the maximum anthesis for the species. Except for the one in and around Memphis (Henry and Herring<sup>1</sup>), none of the surveys gives any idea as to whether the dates indicated (e.g., March-May) refer to the anthoperiod during a given year or to the extreme dates of blooming over a period of several years. In our survey of herbaceous plants in New Orleans (Penfound, Efron, and Morrison<sup>3</sup>), our dates referred to one year's observations only. In the present paper our anthoperiods have been compiled from six years of observations over a fourteen-year span.

The New Orleans area possesses a semi-tropical, coastal climate, due to its position (29°57'N and 90°4'W) and its proximity to the Mississippi River, to Lakes Pontchartrain, Borgne, and Salvador, and to the Gulf of Mexico. It has a mean annual temperature of 69.6° F., a mean annual rainfall of 59.84 inches, and a frostless season of 322 days (January 28 to December 16, inclusive). Conditions for plant development, therefore, are excellent throughout most of the year. Since the average temperature

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for January (our coldest month) is 54.3° F., and since killing frosts may be absent, even in January, some species are found in bloom every day of the year.

The biotic seasons in the New Orleans area do not correspond with the usual climatic seasons. Penfound, Efron, and Morrison<sup>3</sup> designated January, February, and March as the winter season for the New Orleans area. In a paper on the marshes of Louisiana, Penfound and Hathaway<sup>4</sup> recognized six seasons, as indicated in the accompanying list:

<i>Seasons</i>	<i>Recommended Changes</i>
Hiemal (Dec., Jan.)	No winter season
Prevernal (Feb., Early March)	(Jan., early Feb.)
Vernal (Late Mar., Apr.)	(Late Feb., Mar., Apr.)
Estival (May, June, July)	No change
Autumnal (Aug., Sept.)	No change
Postautumnal (Oct., Nov.)	(Oct., Nov., Dec.)

On the basis of the study of the anthoperiods of trees and a comparison of the temperatures of our three coldest months. (December, January, February) with the monthly temperatures at Chicago (Table II), we have disallowed the winter season for the New Orleans area. According to our classification, spring (prevernal and vernal) would extend from January through April; summer (estival) would include May, June, and July and autumn (autumnal, postautumnal) would extend from August through December.

#### METHODS

The survey here presented includes the results of six years of observations, beginning in 1930 and ending in 1943. Although our records included data on seventy-five species of trees, shrubs, and woody vines, approximately one-half of the species were insect-pollinated. Of the remaining thirty-four species, several were too rare, and our records on others were too few for detailed inclusion in our survey. All of the fourteen species included in Figures 1 and 2 are represented by at least three observations and most of them by five or six annual records.

In practice we obtained data only on the woody plants in Audubon Park and on the campus of Tulane University. Records were taken at weekly intervals throughout the blooming period on all possible phenological phenomena. To expedite the taking of notes in the field we prepared the following list of symbols: *B*, bud; *L*, leaf; *F*, flower; *S*, fruit. By using small letters for the initial or final stages for a given phenomenon it was relatively easy to enter the various phenological stages (e.g., bFs would indicate that no leaves had yet appeared, that some buds were still opening, flowering was at its height and some fruits were already set). All records were taken on a tabular form (on 8½x11 paper) prepared in advance of the field work. From these sheets it was very simple to determine the anthoperiods for the common trees in the city.

As an aid in comparing the annual records for a given species, line

# ANEMOPHILOUS TREES—PENFOUND

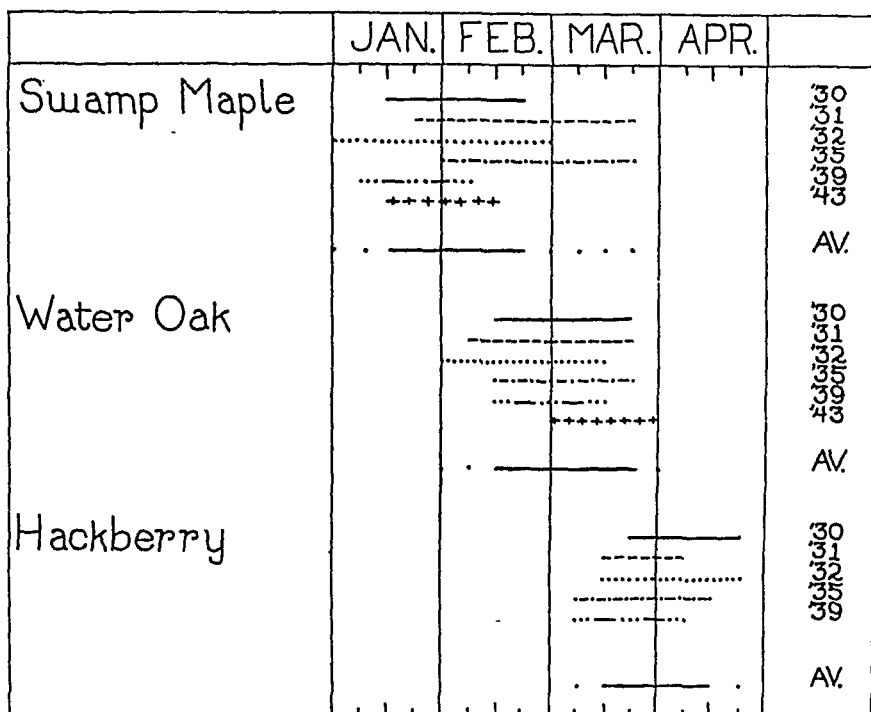


Fig. 1. Annual records of the anthoperiods of three representative anemophilous trees in New Orleans.

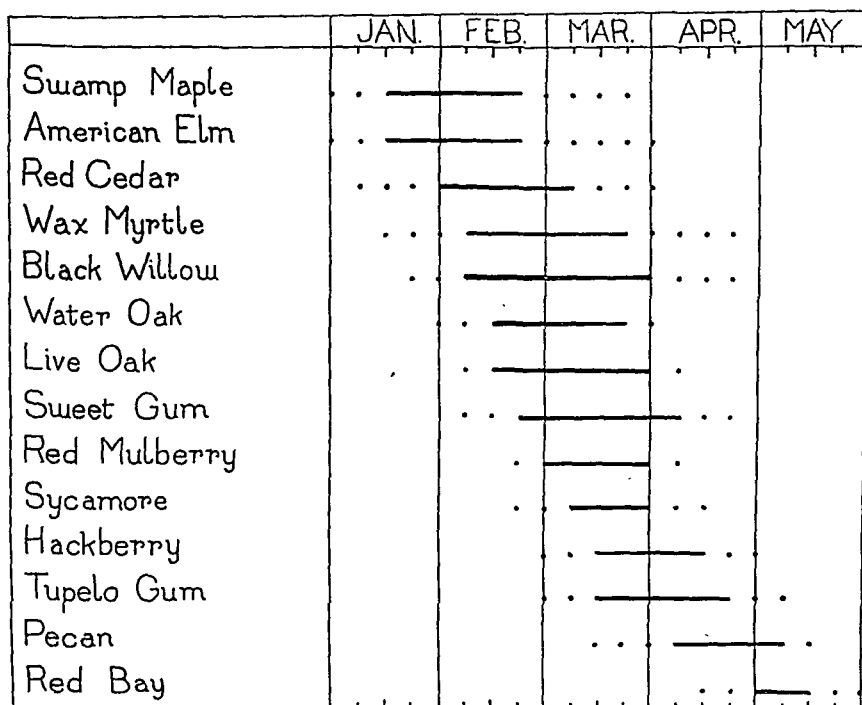


Fig. 2. Normal (solid lines) and unusual (dotted lines) anthoperiods of common anemophilous trees in New Orleans.



# ANEMOPHILOUS TREES—PENFOUND

TABLE I. ANTHOPERIODS OF UNCOMMON TREES IN NEW ORLEANS OR OF TREES ON WHICH ONLY ONE TO THREE ANNUAL RECORDS WERE AVAILABLE

Common name	Scientific name	Weeks of flowering
Bald cypress	<i>Taxodium distichum</i>	Jan. I —Feb. II
Arbor vitae	<i>Thuja orientalis</i>	Jan. III —Apr. II
Sandbar willow	<i>Salix interior</i>	Feb. I —Apr. II
Cryptomeria	<i>Cryptomeria japonica</i>	Feb. I —Mar. IV
Laurel oak	<i>Quercus laurifolia</i>	Feb. I —Mar. III
Cottonwood	<i>Populus deltoides</i>	Feb. I —Mar. I
Swamp oak	<i>Quercus schneckii</i>	Feb. II —Mar. II
Winged elm	<i>Ulmus alata</i>	Feb. II —Mar. II
Green ash	<i>Fraxinus lanceolata</i>	Feb. III —Apr. III
Ash-leaved maple	<i>Acer negundo</i>	Mar. I —Mar. IV
Japanese yew	<i>Podocarpus macrophylla</i>	Mar. I —Apr. IV
Paper mulberry	<i>Broussonetia papyrifera</i>	Mar. II —May I
Weeping willow	<i>Salix babylonica</i>	Mar. II —Apr. III
White mulberry	<i>Morus alba</i>	Mar. III —Apr. III
Osage orange	<i>Toxylon pomiferum</i>	Mar. IV —Apr. IV
Camphor	<i>Cinnamomum camphora</i>	Mar. IV —Apr. IV
Hickories	<i>Hicoria</i> spp.	Mar. IV —June I
Privet	<i>Ligustrum japonicum</i>	Apr. IV —June I
Chinese tallow	<i>Sapium sebiferum</i>	May I —June I
Sugar maple	<i>Acer saccharum</i>	May I —May IV

graphs were utilized (Fig. 2). The species which bloomed earliest were placed at the top and plants with progressively later anthoperiods were placed lower in the table. Complete annual records for only three representative species of the total of 14 species are included here (Fig. 1). However, the average annual anthoperiod (solid part of line) and the unusual extension of the anthoperiod (dotted part of line, one dot per week) have been calculated for each species (Figs. 1 and 2).

## RESULTS

As heretofore stated, detailed records are presented on fourteen species only. Of the other twenty trees bald cypress is the first to flower. The greatest number of species inaugurate anthesis in February but more species are in bloom in mid-March than at any other time (Table I, Fig. 2). Of interest is the fact that different species in a given genus inaugurate flowering at very different times (Table I). For example, swamp maple begins to flower in early January, the ash-leaved maple in early March, whereas the sugar maple does not flower until early May. These facts suggest that both the genus and species names should be included in all plant and pollen surveys.

The records on the more common trees are presented in Figures 1 and 2. The prevernal period (January, early February) is ushered in by the blooming of the swamp maple, *Acer drummondii*, and American elm, *Ulmus americana*. A considerable number of species begin to bloom during the prevernal period but do not reach the middle of their antherperiod until the vernal period. The following eleven species should be assigned to the vernal period: red cedar, *Juniperus virginiana*; wax myrtle, *Myrica cerifera*; black willow, *Salix nigra*; water oak, *Quercus nigra*; live oak, *Quercus virginiana*; sweet gum, *Liquidambar styraciflua*; red mulberry, *Morus rubra*; sycamore, *Platanus occidentalis*; hackberry, *Celtis mississippiensis*; tupelo gum, *Nyssa aquatica*; and pecan, *Hicoria pecan*. Only the red bay, *Tamala pubescens*, may be assigned logically to the estival (summer) period.

It will be noted (Figs. 2 and 3) that all but one of the species (red bay) may be found in blossom during the third week in March. If we employ the usual periods of anthesis (solid part of line) as a basis, nine of the fourteen species were found in bloom during this same period. By coincidence, the height of anthesis of trees in New Orleans occurs near the spring equinox at a time when the first trees are beginning to bloom in the northern states. With us the spring equinox is not the beginning of spring but rather the middle (or a little past the middle) of the biological spring season.

It will be observed that most of the species have completed their anthesis by May 1 (the end of the spring period), despite the fact that the height of anthesis was reached during the middle of March. This means that two and one-half months are required to reach the height of the blooming period but that only one and one-half months are necessary for its completion. This is due to the fact that the first two and one-half months are not only cooler than the subsequent period but also that extended cold periods (sometimes including killing frost) may be present to suspend or decelerate the blooming of the trees which are active at the time.

This is reflected in the antherperiods of the early blooming and late blossoming trees. In general, those species which begin their anthesis early have a longer pollinating season than the later species. The first five species to start to bloom (swamp maple, American elm, red cedar, wax myrtle, and black willow) have very long potential antherperiods (from ten to thirteen weeks), whereas those which inaugurate anthesis after February 15 have antherperiods ranging from six to ten weeks. Swamp maple, water oak and hackberry, which are representative of the early, medium, and late species, have potential antherperiods of eleven, eight and six weeks, respectively (Fig. 1). The actual antherperiod of a given species also varies from year to year; e.g., in 1932, the swamp maple bloomed for eight weeks, whereas it flowered for only four weeks in 1939. Extended flowering occurs when early warm periods are followed by recur-

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TABLE II. TEMPERATURE DATA AT CHICAGO, MEMPHIS, AND NEW ORLEANS  
Degrees Fahrenheit

Average monthly temperatures						
	Jan.	Feb.	Mar.	Apr.	May	June
Chicago	24.3	25.9	35.6	46.7	57.0	66.9
Memphis	41.0	43.6	52.6	61.8	70.4	78.0
New Orleans	54.3	56.8	63.1	68.7	75.2	80.8

Difference between average monthly temperatures						
	Jan.	Feb.	Mar.	Apr.	May	June
Chicago < Memphis	16.7	17.7	17.0	15.1	13.4	11.1
Memphis < New Orleans	13.3	13.2	10.5	6.9	4.8	2.8
Chicago < New Orleans	30.0	30.9	27.5	22.0	18.2	13.9

rent cold spells sufficient to decelerate or to terminate anthesis. Conversely, telescoped anthesis occurs when cold weather, sufficient to prevent the initiation of flowering, is followed by a relatively long warm span.

The relative constancy in the initiation and termination of anthesis from year to year is an interesting one. In general, the variation is considerable for those that initiate their anthesis in early January but relatively constant for those that bloom after the middle of February (Fig. 1). In the (early) swamp maple, the beginning of anthesis varied four weeks and the end of the blooming period varied as much as six weeks. The (late) hackberry, however, exhibited equivalent variations of only one and two weeks each. It will be noted (Fig. 1) that the swamp maple began to bloom on January 1, 1932, but did not initiate anthesis until February 1, 1935. The hackberry, however, initiated blossoming only one week later in 1932 than it did in 1935. It is evident from these facts, that whereas the early species may be ahead of or behind their normal schedule in a given year, the later species are not necessarily influenced in the same direction.

It is customary for the public to refer to early, normal, or late spring seasons. These statements have been based on weather, as well as on the phenology of plants and animals. If based on the trees that began to bloom in January, then 1932 had an early vernal period, but 1935 possessed a late spring season. However, if based on species that inaugurated anthesis in February or March, no such conclusion can be reached (Fig. 1). This means that spring may be early or late for certain species but not necessarily for other and later species. This is due to the great variability in the New Orleans weather during January, February, and March. If January is warm, people are apt to speak of an early spring, whereas if January is cold, and trees do not bloom until February, the public is apt to refer to the spring as a late one. We believe, however, that it is

# ANEMOPHILOUS TREES—PENFOUND

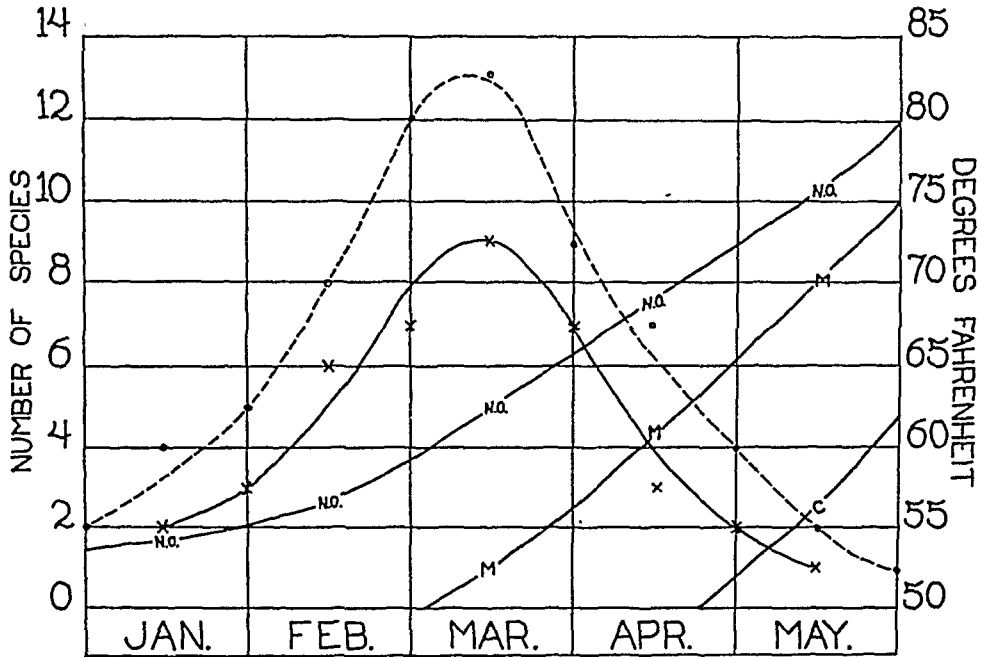


Fig. 3. Relation of number of anemophilous trees in flower to the average monthly temperature at New Orleans. Lines from lower left to upper right represent mean monthly temperatures at New Orleans (N.O.), Memphis (M.), and Chicago (C.).

undesirable to speak of early or late springs and that it is dangerous to utilize the anthoperiods of the early species to anticipate the inauguration of anthesis for the later species.

That the blooming of trees occurs early in the growing season is recognized by all allergists. In New Orleans the height of their anthesis is reached by the middle of March, long before the average temperatures have reached a maximum. An examination of the data in Table II and Figure 3, reveals the fact that the height of anthesis occurs at an average monthly temperature of 63.1° F., which is much closer to the average January temperature (54.3° F.) than it is to the long-term June figure (80.8° F.). This indicates that factors other than temperature are important in the inauguration of anthesis in trees.

## COMPARISON OF ANTHESIS IN CHICAGO, MEMPHIS, AND NEW ORLEANS

The flowering of trees is initiated in early January at New Orleans but is progressively later northward. According to Vaughan<sup>6</sup> it is about two weeks later at each of the following cities: Montgomery (middle January), Memphis (early February), Washington, D. C. (late February), Baltimore (early March), New York (late March) and Boston (early April). It will be noted that the tree season is ushered in one month later at Memphis, two months later at Baltimore, and three months later at Boston when compared with the blooming of trees at New Orleans.

It will be recalled that we concluded that New Orleans did not experi-

# ANEMOPHILOUS TREES—PENFOUND

TABLE III. LOCATION DATA FOR CHICAGO, MEMPHIS, AND NEW ORLEANS

	Latitude	Longitude	Altitude	Mi. North
Chicago	41°53' N	87°36' W	598 ft.	480
Memphis	35° 8' N	90° 5' W	274 ft.	350
New Orleans	29°57' N	90° 4' W	5 ft.	—

ence a true winter season since some species were in bloom throughout the year. This conclusion is supported by a comparison of the average monthly temperatures in New Orleans with those in Memphis and Chicago. The average monthly temperature for January in New Orleans (54.3° F.) is similar to that for March in Memphis (52.6° F.) and to that for May in Chicago (57.0° F.) (Table II). It will be noted, however, that there is only a slight difference between the June temperatures for the three cities (Table II). This means that New Orleans has an extended biological spring season (four months) as compared to those at Memphis and Chicago (about two and one-half months).

An examination of the data in Table II reveals the fact that there is a progressive decrease in the diversity of average monthly temperatures between the three cities with the advance of the growing season. It will be observed, also, that the diversity in temperature is less between New Orleans and Memphis than between Memphis and Chicago and that these differences are nearly eliminated by June. By July, the temperatures in all three cities are very similar. The relative constancy in monthly temperature at New Orleans emphasizes the fact that New Orleans possesses a coastal climate, whereas Memphis and Chicago possess continental climates.

The thermal conditions in these three cities are a product of latitude, altitude and proximity to water. In discussing this problem, it should be observed that we have selected cities with nearly the same longitude, which may be also a factor in the determination of isothermal lines (Table III). Speaking in round numbers, the latitudes of New Orleans, Memphis and Chicago are 30, 35, and 42 degrees north latitude, respectively. This gives a smaller difference between New Orleans and Memphis (5°) than between Memphis and Chicago (7°). These facts are in accord with the temperature differences previously indicated. It will be noted that there is a progressive increase in altitude from New Orleans northward (Table III). In round numbers, Memphis is 300 feet higher than New Orleans and Chicago is 300 feet higher than Memphis. The proximity of New Orleans and Chicago to large bodies of water causes higher winter temperatures and lower summer temperatures than might be expected. Furthermore, the frostless season for both cities is somewhat longer than would be anticipated.

It is common knowledge that trees bloom later with increased latitude

# ANEMOPHILOUS TREES—PENFOUND

TABLE IV. THEORETICAL RETARDATION OF ANTHESIS AT CHICAGO AND MEMPHIS

	Days later due to:		Days Total
	Latitude	Altitude	
Chicago < Memphis	28	3	31
Memphis < New Orleans	20	3	23
Chicago < New Orleans	48	6	54

TABLE V. DIFFERENCES IN INITIATION, TERMINATION AND LENGTH OF POLLINATING SEASONS BETWEEN NEW ORLEANS, MEMPHIS AND CHICAGO

	Difference in weeks		
	Begin earlier	End earlier	Longer
New Orleans > Memphis	5	1	4
Memphis > Chicago	4	4	0
New Orleans > Chicago	9	5	4

and altitude but the principle connected with the delay is not generally known. According to the bioclimatic law (Hopkins<sup>2</sup>) the variation in the time of occurrence of a given periodical event in life activity in temperate North America is at the general rate of four days to each degree of latitude, 5 degrees of longitude and 400 feet altitude, later northward, eastward, and upward in the spring and early summer, and the reverse in late summer and autumn. Concerning our own problem, then, we should expect a lag of four days for each degree of latitude (app. 69 miles) northward and one day each for each 100 feet of altitude. Theoretically, the anthesis of any tree species should be twenty-three days earlier in New Orleans than in Memphis and fifty-four days earlier than in Chicago (Table IV). Here again, it should be noted that the theoretical difference in phenology between New Orleans and Memphis is less (twenty-three days) than between Memphis and Chicago (thirty-one days). This compares closely with the temperature data previously discussed (Table IV).

The actual comparison of anthoperiods of trees in the three selected cities is not so simple as might be anticipated. In the first place, it is a bit dangerous to correlate data based on six years' records at New Orleans with the data at Memphis which are based on two years' observations only and with the data at Chicago which are based on the general records of three local botanists. If we assume that the data at all the stations are representative, then three striking facts are evident. On an average, the trees in New Orleans initiate anthesis at least five weeks earlier than at Memphis and nine weeks earlier than at Chicago. They terminate

# ANEMOPHILOUS TREES—PENFOUND

TABLE VI. POTENTIAL ANTHOPERIODS OF REPRESENTATIVE ANEMOPHILOUS SPECIES IN NEW ORLEANS, MEMPHIS, AND CHICAGO  
All periods in weeks

Species	New Orleans	Memphis	Chicago
Swamp maple	11	6	5
American elm	12	6	5
Red cedar	11	4	6
Sweet gum	10	4	—
Sycamore	8	4	4
Hackberry	8	5	—
Average	10	5	5

flowering one week earlier than the same species at Memphis and only five weeks earlier than at Chicago. This means that the total anthoperiods of the trees at New Orleans are much longer (about double) than those of the same species at Memphis and Chicago (Table VI). If the flowering span is based on six representative species (Table VI), the average anthoperiods per species for New Orleans, Memphis, and Chicago, are ten, five and five weeks, respectively. Stated otherwise, the extended period of flowering at New Orleans is telescoped at Memphis and Chicago—presumably due to the relatively rapid elevation of temperature in late February and early March at the more northerly cities. In general, the pattern of anthesis is very similar at Memphis and Chicago. Although pollination begins four weeks earlier at Memphis it also ends four weeks sooner, thus giving anthoperiods of about the same length at the two cities.

The determination of the height of anthesis from the data collected is very precarious. Presumably it might be midway between the start and the end of the blooming period. It will be recalled, however, that, for the trees as a group in the New Orleans area, ten weeks are required to reach the height of anthesis but only six weeks are necessary for its completion. This is true also for individual species. In a given season the average anthoperiod per species is four to eight weeks but the height of blossoming is usually not reached until well past the midpoint. This condition is due to the prevalence of cool weather during the earlier part of the anthoperiod. Occasionally, this situation is reversed if warm weather in the early part is followed by unseasonably cold weather in the later segment of the anthoperiod. Presumably, the height of blossoming would be nearer the midpoint in Memphis and Chicago where the flowering is telescoped into a much shorter period. It should be obvious, however, that a person would be rather presumptuous to attempt to compare the heights of the blooming periods at different cities until more data are at hand.

A comparison of the observed and theoretical data on the initiation

## ANEMOPHILOUS TREES—PENFOUND

of anthesis is of some interest. Theoretically, a given species of trees in New Orleans should bloom twenty-three days earlier than at Memphis and fifty-four days earlier than at Chicago. Actually, our species average about thirty-five days earlier than at Memphis and sixty-three days earlier than at Chicago. Presumably this is because we have no winter season from a biological standpoint. The blossoming of trees is initiated at Memphis and Chicago before the average monthly temperature reaches  $45^{\circ}$  F. Since our lowest average mean monthly temperature is not lower than  $54.3^{\circ}$  F., it is obvious that winter does not come to New Orleans.

### SUMMARY

1. The results of six years of observations on the pollination of anemophilous trees in New Orleans are presented herein.

2. New Orleans possesses a semi-tropical, coastal climate with a mean annual rainfall of 59.8 inches, a mean annual temperature of  $69.6^{\circ}$  F. and a frostless season of 322 days.

3. New Orleans lacks a winter season, since some plants are in bloom every month of the year and since our coldest month has an average temperature ( $54.3^{\circ}$ F) well above the minimum monthly temperature necessary for the anthesis of trees.

4. The anthesis of trees is limited largely to the biological spring season (January, February, March, April), the height of flowering being reached at the spring equinox.

5. Trees which inaugurate anthesis in January possess relatively longer anthoperiods and also exhibit greater variability in the initiation and termination of anthesis than trees which begin to flower later in the spring.

6. The variability in the weather and in the anthesis of trees is so great at New Orleans that it is illogical to speak of early or late spring seasons.

7. New Orleans possesses an extended biological spring season (four months) as compared to Memphis and Chicago (two and one-half months).

8. On an average the trees in New Orleans possess potential anthoperiods about twice as long (ten weeks) as those at Memphis (five weeks) and Chicago (five weeks).

9. Theoretically, the initiation of anthesis of a given tree species at New Orleans should be twenty-three days and fifty-four days earlier whereas species actually average about thirty-five days and sixty-three days earlier, respectively, than those at Memphis and Chicago.

### SUMARIO

1. Se presentan los resultados de seis años de observación sobre la polinación de árboles anemófilos en Nueva Orleans.

2. Nueva Orleans posee un clima costero semi-tropical con una caída



## ANEMOPHILOUS TREES—PENFOUND

de lluvia anual de 59.8 pulgadas término medio, una temperatura media anual de 69.6° F. y una estacion de 322 dias sin heladas.

3. Nueva Orleans carece de invierno desde que las plantas florecen todos los meses del año y desde que el mes mas frio tiene una temperatura media de (54.3°F.) bastante mas alta que la temperatura mínima mensual necesaria para la antesis o florescencia de los árboles.

4. La antesis de los árboles está limitada mayormente a la estación biológica de primavera (enero, febrero, marzo, abril) siendo alcanzada la mas alta florescencia en los equinoccios de la primavera.

5. Los árboles que principian su antesis en enero, poseen relativamente antoperiodos mas largos y presentan tambien mas grande variabilidad en la iniciación y terminación de la antesis que los árboles que empiezan a florecer mas tarde en las primavera.

6. En Nueva Orleans la variabilidad en el tiempo y en la antesis de los árboles es tan grande que no es posible hablar de temprana o tarde primavera.

7. Nueva Orleans posee una primavera biológica prolongada (4 meses) comparada con Memphis y Chicago (2 meses y medio).

8. Por término medio los árboles en Nueva Orleans poseen potencial antoperiodos el doble mas largo (10 semanas) que los de Memphis (5 semanas) y Chicago (5 semanas).

9. Teoricamente la iniciación de la antesis de una dada especie de árboles en Nueva Orleans, debia ser 23 dias y 54 dias antes, pero actualmente estas especies dan un promedio de 35 dias y 63 dias respectivamente, antes que los en Memphis y Chicago.

### ACKNOWLEDGMENTS

The author wishes to express his appreciation to Dr. Henry S. Conard, Mr. Charles C. Deam, and Dr. L. H. Tiffany for data on flowering in the Chicago area, to Dr. B. G. Efron for suggesting the problem and to various students at Tulane University who have helped in the collection of data.

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## SEVERE URTICARIAL REACTION DUE TO POOLED HUMAN PLASMA†

### Report of Case

CAPTAIN BERNARD DICKSTEIN, M.C., A.U.S., F.A.C.A.

Camp McCoy, Wisconsin

POOLED human plasma is now being used in such unparalleled quantities and with such apparent safety that any unfavorable and serious result from its use should be reported. At this writing, July, 1943, only one other case of allergic reaction due to pooled human plasma has been reported in the literature.

### REPORT OF CASE

*History.*—A soldier, white, aged twenty-four, was admitted at 0330 May 3, 1943, to the Station Hospital, Camp McCoy, Wisconsin, with a knife wound of the right lower abdomen, left arm, and left thigh. These injuries occurred after a period of moderate drinking.

Seven and one-half hours after entry into the hospital an exploratory laparotomy was done under pontocaine spinal anesthesia and a perforation of the ileum was repaired.

Significant events occurred as follows:

1102—Spinal anesthesia instituted with 150 mgm. of pontocaine. 50 mgm. of ephedrine sulfate given intramuscularly.

1110—Operation begun.

1115—An intravenous setup connected and 5 per cent glucose in saline allowed to drip in slowly.

1130—250 c.c. of human pooled plasma from Pool 109 was connected with the intravenous tube and allowed to flow in by gravity. The wound in the ileum had been located and sutured, and closure procedure was begun.

1155—The patient complained of itching just before closure of the peritoneum. Welts, which quickly became confluent, were noticed over his face and body, and he became cyanotic. The plasma was immediately discontinued. Approximately one-half, or 125 c.c. had been given.

1205—Ephedrine sulfate, 50 mgm. given intramuscularly.

1210—4 minims of epinephrine given intravenously and 6 minims intramuscularly. By now the patient's body was one mass of welts, he was deeply cyanosed, and respirations ceased. Artificial respiration was instituted at once.

1216—Coramine, grains  $1\frac{1}{2}$ , given intramuscularly.

1221—Oxygen inhalation started.

1230—Spontaneous respirations reestablished, but oxygen was continued off and on for another ten minutes. During this interval the patient became less cyanosed and the welts diminished in prominence.

1252—All cyanosis had disappeared. There was no further respiratory difficulty, and the welts disappeared leaving a residual erythema.

He thereafter pursued an uneventful course and was discharged from the hospital June 8, 1943.

*Investigation of Allergic Factors.*—Additional examination of the patient was made on the sixteenth day after operation. No allergic tendencies were elicited

†The pooled human plasma used was prepared by the Blood Plasma Center at LaGarde General Hospital, New Orleans, Louisiana. It is a liquid plasma containing dextrose solution and a 1 per cent merthiolate solution as preservatives.

## SEVERE URTICARIAL REACTION—DICKSTEIN

in his family or in his past history. Significant illnesses were "quinsy" sore throat in 1938, and severe "athlete's foot" in 1941, requiring bed rest for relief. The general physical examination was essentially negative. The abdominal operative wound was healing well. Constitutionally, the patient was the broad, short type of

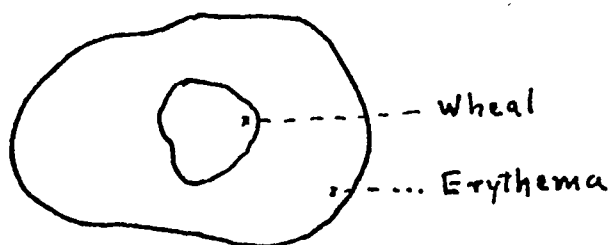


Fig. 1. Results of one of two intradermal tests on patient with .05 c.c. of pooled human plasma from Pool 109. The other reaction was identical. Figure shows size of wheal and of zone of erythema.

individual, rather florid, who perspired easily and exhibited vasomotor instability. No dermatographism could be demonstrated.

The investigation was along two lines:

(1) To show that this urticarial reaction satisfied the criteria of an allergic reaction: a sensitized individual with circulating antibodies which could be passively transferred and which would react with some one of the substances administered during the operation.

(2) To identify those substances or antigens which could bring on such a reaction, and to show what was the most likely causative agent.

The following investigative steps were taken in the order listed:

1. A check of blood and urine reports showed no signs of hematuria, hemoglobinuria, or anemia. Therefore, hemolysis as the result of the interaction between agglutinins and red blood cells was ruled out.

2. Since anaphylactic antibodies and precipitins occasionally appear in the human circulation following anaphylactic-like reactions, a test was made for precipitins in the patient's circulation against the plasma used at the operation. This was done by the ring test in which small amounts of the patient's serum were carefully overlaid with various dilutions of the Pool 109 plasma. No ring appeared with the patient's serum or with the serum of a control. The test was considered evidence that there were no anaphylactic antibodies or precipitins in the patient's circulation for the plasma used at operation.

3. Tests to determine the state of reactivity of the patient's skin were next done. This is important in evaluating any further skin tests. A hyper-reactive skin will give a maximum response to a minimal irritation.

A drop of 1/1000 histamine phosphate was worked into the patient's skin by the multiple puncture method as in smallpox vaccination. Within several minutes a wheal 4 mm. in diameter appeared surrounded by a zone of erythema 7 mm. in diameter. The reaction subsided within twenty minutes. This was considered to be well within the range of normal skin reaction to histamine, as observed on other subjects.

Attempts to elicit signs of dermatographism by stroking the skin with a tongue blade had given no response beyond an erythema.

It was concluded that the skin of the patient was not hyper-reactive and that any positive skin tests obtained could be regarded as proper evidence of the degree of skin sensitivity to injected allergen.

4. Test for pontocaine sensitivity was made by an intradermal injection of a concentrated solution pontocaine (100 mg. of pontocaine dissolved in 25 c.c. of

## SEVERE URTICARIAL REACTION—DICKSTEIN

physiological saline, 0.05 c.c. of this solution injected). No reaction occurred at the site of injection.

5. Tests of the skin of the patient and of control subjects with various lots of pooled human plasma were made to determine whether the patient alone gave a

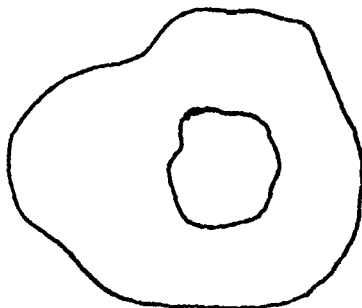


Fig. 2. Reaction to intradermal test on patient with .05 c.c. of pooled human plasma from pilot bottle of Pool 109, sample of which was received from Blood Plasma Center, La Garde General Hospital, New Orleans, Louisiana. Figure shows size of wheal and erythema.

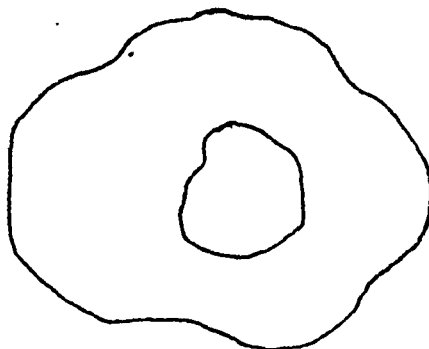


Fig. 3. Intradermal test on patient with .05 c.c. of pooled human plasma from Lot 109A. The large wheal and erythema were accompanied by itching.

positive reaction to Pool 109 plasma, and also whether he gave reactions to other pooled plasma as well.

Intradermal tests were done on the patient using 0.05 c.c. of various lots of pooled human plasma. The reactions obtained are reproduced diagrammatically in full scale. Two separate tests with the Pool 109 plasma used on the patient gave wheals 2 cm. and erythema zones 4.5 cm. in diameter (Fig. 1). The sample from the pilot bottle of Pool 109 gave a wheal 1.5 cm. in diameter and a zone of erythema 3.5 cm. in diameter (Fig. 2). The test with Lot No. 109-A from Pool 109 showed a similar reaction (Fig. 3), the wheal measuring 1.75 cm. and the zone of erythema 4 cm. in diameter. All Pool 109 tests were accompanied by marked itching, and persisted for longer than an hour.

Intradermal tests on the patient with samples from Lot 104-E (Fig. 4) and Lot 105-A (Fig. 5) showed smaller reactions. The wheals were 0.75 cm. in diameter, without zone of erythema, and without itching.

The reactions with Pool 109 were interpreted as allergic, and those with other pools as nonallergic.

Additional tests on controls with pooled human plasma from Pool 109: Controls were three of the enlisted personnel who offered their services for the investigation; 0.05 c.c. of the plasma was injected intradermally into each. The re-

## SEVERE URTICARIAL REACTION—DICKSTEIN

action on all three was similar. There was no zone of erythema, no itching sensation, and the wheals averaged 0.8 cm. in diameter.

These reactions demonstrated that no allergy to Pool 109 plasma existed in the controls.



Fig. 4. Reaction to intradermal injection on patient with 0.05 c.c. pooled human plasma from Lot 104 E. A small wheal was present without erythema or itching.



Fig. 5. Reaction to intradermal injection on patient with 0.05 c.c. pooled human plasma from Lot 105 A. There was no erythema and no itching sensation.



Fig. 6. Reaction of intradermal tests with 0.05 c.c. pooled human plasma from Lot 109 on one of the three controls. There was no erythema or itching sensation and very small wheal formation. Reactions on the other two controls with the same plasma were approximately the same.

Figure 6 illustrates one of the reactions and shows its similarity to the intradermal test reactions on the patient with plasma from pools other than Pool 109.

These tests showed that the patient gave a positive test to Pool 109 plasma, and that he gave no positive allergic type of skin reaction to any of the other pools tested.

6. Passive transfer tests of the Prausnitz-Küstner type were done by injecting intradermally 0.1 c.c. of the patient's serum into two subjects and twenty-four hours later testing these sites, and noninjected control areas, with 0.05 c.c. of Pool 109 plasma.

Neither of the two subjects exhibited an allergic response in the nonsensitized areas injected for control purposes.

The two subjects (Figs. 7 and 8) after ten minutes showed definite allergic type of skin reactions in the sensitized areas. The wheals measured 12 and 11 mm. in diameter, with zones of erythema, 22 and 25 mm. in diameter; there was itching. Thirty minutes later there was still no reaction in the nonsensitized sites, but the reactions in the sensitized areas had increased (Figs. 9 and 10), the wheals now measuring 16 and 18 mm. in diameter and the zones of erythema 4 cm. At the end of one hour the reactions in the sensitized areas had diminished and both wheals measured 7 mm. in diameter.

The tests were interpreted as indication of the presence in the patient's blood of allergic antibodies (reagins) against plasma from Pool 109.

The first part of the investigation thus showed that the reaction of the patient was allergic in nature and that it was due to a reaction to some elements in the plasma of Pool 109 alone, and not to plasma per se.

The next half of the problem was the identification of those elements or antigens in Pool 109 plasma which were responsible for the allergic reaction. This was developed as follows:

1. Intradermal skin tests on the patient were done with common allergens to determine allergic tendencies especially in regard to foods.

## SEVERE URTICARIAL REACTION—DICKSTEIN

Reactions were classified in the following manner: a 4 plus reaction was one with a wheal showing several pseudopods and surrounding erythema; 3 plus, a wheal having at least one pseudopod and surrounding erythema; 2 plus, an irregular wheal and erythema; 1 plus, a small smooth wheal and erythema.

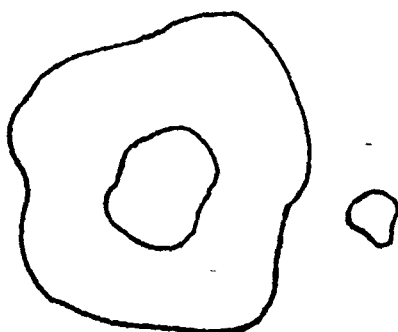


Sensitized Site      Nonsensitized Site  
Fig. 7.—(Subject *A*)

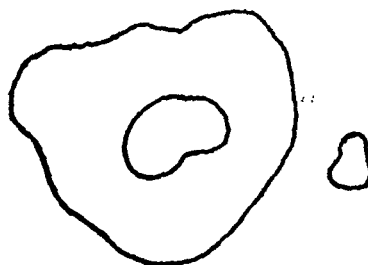


Sensitized Site      Nonsensitized Site  
Fig. 8.—(Subject *B*)

Figs. 7 and 8. Reactions after 10 minutes with Prausnitz-Küstner passive transfer tests on subjects *A* and *B*, using sensitizing serum from patient, and plasma from Pool 109. There are positive reactions in the sensitized sites.



Sensitized Site      Nonsensitized Site  
Fig. 9.—(Subject *A*)



Sensitized Site      Nonsensitized Site  
Fig. 10.—(Subject *B*)

Figs. 9 and 10. Same passive transfer tests as in Figures 7 and 8, thirty minutes later. Reaction in sensitized sites have grown larger.

The allergens used and the results obtained indicated a 4 plus to 2 plus reaction to tetanus toxoid, cocoa, coffee, tea, milk, beef, lamb, timothy, tragacanth, and acacia, and a 1 plus reaction to pork and horse dander. The general picture shown by these intradermal tests was one of multiple skin sensitivity, primarily to foods.

2. Identity of specific antigens in Pool 109 plasma was investigated, using test tube neutralization procedure of Walzer and Bowman combined with passive transfer tests on other subjects.

The experimental basis for this procedure was derived from well-controlled laboratory experiments which have proved that the same antibody which passively sensitizes the skin is inactivated or destroyed by its specific antigen only, when they are incubated together. The use of this fact to determine the identity of an unknown antigen may be illustrated as follows: If we have a sensitive individual who has been shown by skin tests to have circulating in his blood a dozen known antibodies, one of which is the antibody against egg white, and we have an unknown serum to which the sensitized individual gives a positive skin test, the question whether this unknown serum contains egg white or not may be answered by this hypothetical experiment: A quantity of the sensitive individual's serum is incubated for twenty-four hours with a dilution of egg white calculated to react

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with all the egg-white antibody present, if there is any. This incubated material is then injected into a nonsensitized subject's skin; twenty-four to forty-eight hours later this site is tested with an egg-white dilution in the usual manner of a skin test. If there is a negative reaction we have some indication that some of the antigen in the unknown serum is egg white, i.e., no egg-white antibodies were left after

TABLE I. RESULTS OF INTRADERMAL SKIN TESTS ON PATIENT WITH ASSORTED FOODS AND OTHER ALLERGENS

Tetanus toxoid .....xxxx	Corn .....0	Tragacanth .....xx
Horse Dander.....x	Navy Bean .....0	Acacia .....xx
Milk .....xx	Salmon .....0	Tobacco .....0
Egg .....0	Oyster .....0	Coffee .....xxx
Beef .....xx	Whitefish .....0	Cocoa .....xxxx
Pork .....x	Codfish .....0	Orange .....0
Chicken .....0	Shrimp .....0	Timothy 1:1000 dilution.xxxx
Lamb .....xxx	Perch .....0	Ragweed 1:100 .....0
Rye .....0	Trout .....0	Tea .....xx
Wheat .....0	Lobster .....0	Pineapple .....0
Rice .....0	Halibut .....0	Apple .....0
Oat .....0	Crab .....0	Strawberry .....0

incubation to develop passive sensitization. The proof is stronger if sensitized serum alone, not mixed with egg white, is injected at the same time into an adjacent site, this site, twenty-four to forty-eight hours later giving a positive reaction to egg white. The proof is established if, in a third unprepared control site, egg white gives no reaction, thereby showing nonsensitivity of the ordinary skin of the subject to egg white.

A positive reaction in both prepared sites with a negative one in the control site could mean either that there is no egg-white antigen present in the serum, or that not enough egg white had been used or enough time allowed for neutralization of all the antibodies. If the latter possibilities are considered, more time and a stronger dilution of egg white can be used for incubation. Any excess of egg white will have no effect on the test.

The combined passive transfer procedures in this case were accomplished in the following manner:

Equal quantities of the patient's serum and the Pool 109 plasma were mixed and incubated for twenty-four hours. At the end of this time sites were prepared on the arms of three subjects. One row of sites was injected with 0.02 c.c. of the neutralized patient's serum for each site and an adjacent row of sites was injected with 0.01 c.c. of the unneutralized patient's serum for each site. Forty-eight hours later intradermal tests were done on these sites using the antigens to which the patient had reacted most strongly, as indicated in skin tests above, and in each case injecting these antigens into nonsensitized sites as a control measure.

A negative or diminished reaction in the neutralized serum site, a positive reaction in the unneutralized serum site, and a negative reaction in the nonsensitized site would show that during incubation in the test tube the antibody in the patient's serum had been neutralized or destroyed by its corresponding antigen in the plasma, thereby identifying that particular antigen. A positive reaction in the first two sites and no reaction in the nonsensitized site would indicate the presence of antibodies in the patient's circulation for the allergen tested for, but would not show whether or not it was present in the plasma. A negative reaction in all sites would mean either the subject's skin was not receptive to being passively sensitized, or else there were none of the specific antibodies tested for, or an undemonstrable amount of them, present in the patient's circulation. A positive reaction in the nonsensitized sites or in all sites would mean that the subject himself was sensitive to the specific allergen tested with and that the results of that particular test would have to be disregarded.

One of the subjects reacted only to tetanus toxoid in all three rows and was

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Test Allergen	Sensitized sites previously injected with neutralized patient's serum.	Sensitized sites previously injected with patient's unaltered serum.	Nonsensitized sites—no previous injection.
Tetanus toxoid			
Milk			
Beef			
Lamb			
Coffee			
Cocoa			

Fig. 11. Walzer-Bowman and Prausnitz-Küstner passive transfer tests on Subject *A*. Tetanus toxoid gave large allergic type reactions in all sites. Milk, beef, and lamb showed definite erythema and wheal reactions in both neutralized and unneutralized serum sites, but no reaction in control sites. Coffee and cocoa were entirely nonreacting in all sites.

discarded as nonreceptive. The other two demonstrated the results shown in Figures 11, 12, and 13.

Since reactions to tetanus toxoid were present in both subjects in all sites, including the nonsensitized sites, tetanus toxoid was excluded from consideration. Coffee and cocoa gave no reaction on either of the subjects in any of the sites, and were likewise eliminated.

Subject *A* (Fig. 11) gave large, positive, allergic type of reactions to milk, beef, lamb, in both the neutralized and unneutralized serum sites. All were of approximately the same size, the wheals averaging 1.5 cm. and the zones of erythema 3.5 cm. in diameter. There was no reaction in the nonsensitized sites. Thus, so far, because of the positive reactions in both the sensitized sites, Subject *A* gave no proof of any desensitization or destruction of antibodies during incubation. The presence of antibodies against milk, beef, and lamb in the serum of the patient was again demonstrated, but there was no indication whether or not these antigens were present in Pool 109 plasma.

Subject *B* (Fig. 12) supplied the evidence looked for, in that the neutralized serum sites gave no reaction to milk, beef, and lamb, while the unneutralized serum sites gave positive reactions with wheals averaging 12 mm. and the zones of erythema averaging 2.5 cm. There were no reactions in the nonsensitized sites. The conclusion was, therefore, that Subject *B* had demonstrated the presence of the allergens from milk, beef, and lamb in the plasma from Pool 109. Furthermore, Sub-



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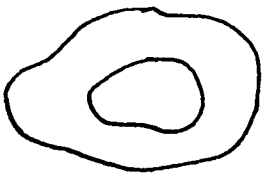
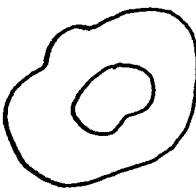
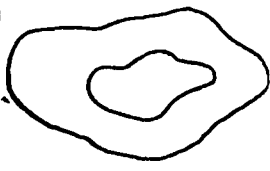















Test Allergen	Sensitized sites previously injected with neutralized patient's serum.	Sensitized sites previously injected with patient's unaltered serum.	Nonsensitized sites—no previous injection.
Tetanus toxoid			
Milk			
Beef			
Lamb			
Coffee			
Cocoa			

Fig. 12. Walzer-Bowman, Prausnitz-Küstner passive transfer tests on Subject *B*. There were large reactions in all sites to tetanus toxoid. Milk, beef, and lamb gave no reactions in the neutralized serum sites or in the nonsensitized sites, but in the unaltered serum sites there were definite wheal and erythema reactions.

ject *B*'s tests demonstrated that the incubation phase of this procedure had been properly carried out and that other reasons would have to be considered for the initial failure on Subject *A*.

Forty-eight hours later further tests were done on the remaining unused sensitized sites on Subject *A*. Milk was used again, and several new allergens. The results with the milk were now the same for Subject *A* as for Subject *B*, i.e., there were no reactions in the neutralized serum site or in the nonsensitized site, but a large reaction in the unaltered serum site. Tragacanth, acacia, and timothy gave little or no reaction and were eliminated from consideration. No reliable explanation can be given for the difference in the reaction to milk on Subject *A* in the two series separated by forty-eight hours. It could be assumed with reason that the presence of desensitization and destruction of the antibody merely took longer with Subject *A* than with Subject *B*.

To summarize, the results of these combined tests as illustrated by Figures 11, 12, and 13, gave proof of the presence of allergens from milk, beef, and lamb in Pool 109 plasma, and of the presence of their specific allergic antibodies in the patient's serum.

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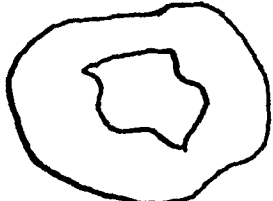

Test Allergen	Sensitized sites previously injected with neutralized patient's serum.	Sensitized sites previously injected with patient's unaltered serum.	Nonsensitized sites — no previous injection.
Tragacanth			
Acacia			
Timothy 1:1000 dil.			
Milk			

Fig. 13. Additional Walzer-Bowman, Prausnitz-Küstner passive transfer tests on Subject A, forty-eight hours after the first series. Here milk gave no reaction in both the neutralized serum and nonsensitized sites, but a definite wheal and erythema reaction in the unaltered serum sites. There were slight or no reactions to tragacanth, acacia, and 1:1000 dilution of timothy pollen.

## DISCUSSION

In general there are two types of serums used for treatment: the animal or heterologous type of serums, called also foreign serums, and, in contrast to these, the homologous or human types of serums, such as the pooled human plasma. In this discussion, the term "serum reaction" is used to indicate those reactions incident to the serums themselves and not due to any pyrogenic factors contributed by the apparatus or to circulatory imbalance.

Serum reactions in human beings are usually the result of the injection of foreign or heterologous serums. The most common is the reaction following the very first injection. This is of the delayed or serum sickness type and is characterized by fever, skin eruptions, and joint symptoms appearing after a definite incubation period. Although it is believed by Vaughan and Tuft and others that the mechanism in these cases is

a cell injury due to the toxicity of the foreign protein, others feel that this is a true allergic phenomenon of the anaphylactic type involving a union of the remaining, circulating antigens with antibodies just being produced. Serum sickness is never fatal.<sup>4,6,7</sup>

Relatively rare, considering the great number of foreign serums constantly being injected, is the more severe and occasionally fatal anaphylactic reaction occurring after a second or re-injection of a foreign serum. Here, in contrast to serum sickness, we have true allergic reaction in an individual sensitized by previous injections with a foreign serum. The reaction comes on within a few seconds or, at the latest, within a few hours. It is characterized by a generalized urticaria and angioneurotic edema, by dyspnea, and by various degrees of shock. Death may result. This type of serum reaction encompasses practically all of the allergic reactions encountered with the use of heterologous types of serums.

The reactions resulting from the injection of human or homologous types of serum are practically all confined to those due to incompatibility of blood types and the interaction of red cells with agglutinins. These are not considered allergic phenomena. *All the remaining reactions with human blood or serum are, in essence, allergic reactions due to allergens of the foreign protein type or their antibodies, transmitted through the medium of the human serums.*

The true allergic reaction with use of homologous types of human blood or serum or pooled plasma is extremely rare, and the occurrence of severe urticarial reaction with shock is almost unique. A search of the literature reveals less than a half dozen, isolated cases of true allergic serum reaction following use of human blood or serum.

Ramirez,<sup>5</sup> in 1919, reported a case of horse asthma in a nonallergic, previously nonasthmatic individual who had received a blood transfusion from a donor suffering from horse asthma. The passive sensitization of this recipient by the introduction into his circulation of allergic antibodies against horse dander resulted in the onset of asthma whenever he came near horses.

Berger<sup>1</sup> reported the occurrence of urticaria in an eighteen-month-old child following the intramuscular injection of blood from an individual sensitive to horse serum (Berger himself). The child had previously been receiving antistreptococcic and normal horse serum.

Duke and Stofer<sup>3</sup> reported a case which approximated in its basic elements the case with which this paper is concerned. Here a woman, who was allergic to milk, was transferred with the blood of a donor who had ingested milk shortly before being bled. The transfusion was followed by a severe serum reaction.

Most recently Colonnell reported in the *U. S. Navy Medical Bulletin* the occurrence of severe urticarial reaction to dried human plasma.<sup>2</sup>

In no one of the cases cited was the reaction due to sensitization to human serum or red cells and the interaction of red cells with agglutinins.

## SEVERE URTICARIAL REACTION—DICKSTEIN

Duke and Stofer's case was the result of the introduction of an excess amount of allergen (e.g., milk), contained in the blood of the donor, into a recipient's blood.

Our own case belongs in the category of the cases cited above. The proof for this may be summarized from the results of the progressive investigative steps taken:

1. Pontocaine, which had been used for the spinal anesthesia, gave a negative skin reaction even with a highly concentrated solution. It is unlikely that the patient had ever been previously sensitized to it. Moreover, allergic drug reactions are most common following prolonged use of a drug.

2. An examination of the frequent blood and urine laboratory reports, both before and after operation and for the weeks postoperative, had given no indication of hematuria or blood changes following the allergic shock. It was, therefore, presumed that there was no harmful interaction between the patient's red cells and the plasma injected.

3. As was stated previously, antibodies and precipitins are occasionally found in the circulation of human beings following an anaphylactic-like reaction. They are usually found in the blood in equal quantities, and a test for precipitins will indicate the amount of anaphylactic antibodies present. No precipitins could be demonstrated by the ring test. Though this test was crude, it was concluded that no anaphylactic antibodies or precipitins against Pool 109 plasma were present in the patient's serum. Therefore, if it is understood that to demonstrate an anaphylactic reaction one must show the presence of precipitins, it can be said that no anaphylactic shock reaction is demonstrated here.

4. Intradermal skin tests on the patient with plasma from several pools including Pool 109 showed that he was allergic only to the plasma from Pool 109 and not to the other plasma pools available for testing. These same tests on control subjects showed that the patient alone gave allergic skin reactions to Pool 109 plasma.

5. Intradermal skin tests on the patient with the common allergens gave definitely positive reactions to milk, lamb, beef, coffee, cocoa, and tea, and to tetanus toxoid, tragacanth, acacia, and timothy pollen. On the basis of these reactions the patient was considered an allergic individual with multiple sensitivities.

6. The intradermal, passive transfer tests done on subjects using serum from the patient as sensitizing agent showed: (a) the presence in the blood of the patient of antibodies or reagins for Pool 109 plasma; (b) the presence of allergens from milk, beef, and lamb in Pool 109 plasma; and (c) the presence of their specific allergic antibodies in the patient's serum.

Thus the elements in Pool 109 responsible for the allergic reaction in the patient may be identified, with reasonable assurance, as milk, beef, and lamb. Other allergens than those tested for may have been respon-

## SEVERE URTICARIAL REACTION—DICKSTEIN

sible also, but because these three are such common foods, and milk especially is such a common offender, these are the most probable causes of the allergic reaction.

The question next to be answered is, "How did these antigens get into only Pool 109 plasma?" Experiments by various workers have shown that unaltered proteins are absorbed from the intestinal tract shortly after ingestion of a meal.<sup>1,3,4,5,6,7</sup> Gastro-intestinal disturbances and the drinking of alcohol facilitate the passage of the protein particles through the gastro-intestinal mucosa. It is reasonable to assume, therefore, that a higher per cent of Pool 109 donors, than of other pool donors, by some curious accident, were bled soon after a meal—and that these meals must have been especially ones containing milk, beef, and lamb.

### CONCLUSIONS

1. The severe reaction of the patient was an allergic one due to elements specifically present in Pool 109 plasma and that these elements were antigens from milk, beef, and lamb.
2. That no allergic reaction to human plasma *per se* occurred.
3. The chance of such reactions will be less if (a) blood donors avoid all food for at least six hours before giving blood, and (b) as many donors as possible contribute to a pool in order to dilute such allergens as might be present in individual instances.

### CONCLUSIONES

1. La reacción intensa del enfermo fué debida a alergia y también a elementos específicos presentes en plasma 109 obtenido de diversos individuos, y que estos elementos eran antígenos de leche, carne de vaca y cordero.
2. Que no ha ocurrido reacción al plasma de seres humanos "per se" o individualmente.
3. Las posibilidades de ocurrir tales reacciones se reducen a mucho menos si (a) los donadores de sangre no comen nada durante 6 horas antes de dar la sangre, y (b) si tantos donadores como sea posible contribuyen a la mezcla, para así diluir los alérgenos que puedan existir en estos individuos.

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6. Tuft, Louis: *Clinical Allergy*. Revised edition. Philadelphia: W. B. Saunders Co., 1938.
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# CONTACT DERMATITIS FROM RUBBER GAS MASK

CAPTAIN JOE C. GILBERT, M.C., A.U.S.

In looking through the literature, sixteen cases of contact dermatitis to rubber gas masks were recorded in the *British Medical Journal* and one case in the *Journal of the American Medical Association*. The following case differs from those published in that it represents four recurrent attacks of contact dermatitis, each reaction more severe than the former.

## REPORT OF CASE

A soldier\*, aged forty, entered the Army August 29, 1942. Three weeks later he wore a gas mask while in a gas chamber. In three hours the patient experienced an acute burning and itching of the face. A mild erythematous dermatitis of the peripheral portion of the face developed which persisted for twenty-four hours. Two weeks later he wore the same gas mask and a similar dermatitis developed but lasted for one week. Following this attack the mask was soaked in a soap solution and cleansed. Seven weeks after his entrance into the Army, October 1942, he participated in a gas mask drill in Atlanta, Georgia, wearing the same gas mask. The third attack of dermatitis occurred, this time for a duration of six weeks. The only therapy consisted of local applications of calamine lotion. On February 10, 1943, he wore the same gas mask on a hike. Within ten minutes he was forced to remove the mask because of the severe burning of his face.

On February 11, 1943, the patient was hospitalized and was referred for allergy consultation two days later. Prior to admission there was a generalized erythema of the peripheral portion of the face which touched the mask. The following day there was scaling and vesiculation. Crusts soon appeared and the accompanying picture was taken five days after the exposure to the contact which necessitated his admission to the hospital.

His face was treated with a soothing lotion, lime water and olive oil mixture. The crust formation ceased in two weeks.

Personal and familial histories of allergic diseases and dermatitis were non-contributory except for a few areas of vitiligo on the patient's chest and left arm. The patient had never experienced a contact dermatitis previously, although he had handled many rubber products. The blood count and urinalysis were normal; serology was negative.

Patch tests were applied to the patient's arms and back for a period of forty-eight hours. The gas mask rubber used in testing was obtained from a mask identical to that worn by the patient.

## RESULTS OF PATCH TESTS

Readings following forty-eight hours of contact with the patch tests.

1. Gas mask rubber—third grade reaction (erythema, small vesicles, and slight edema at local test site).
2. Adhesive tape—delayed second grade reaction (erythema and papules at local test site).
3. Rubber sheet—Negative.
4. Dark rubber band—Negative.
5. Light rubber band—Negative.
6. Red rubber band—Negative.
7. Mercury bichloride (0.1 per cent)—Negative.
8. Copper sulfate (5 per cent)—Negative.
9. Formalin (5 per cent)—Negative.
10. Resorcin (10 per cent in 95 per cent ethyl alcohol)—Negative.

Five days after admission to this hospital, crust was heavily formed on the patient's face. There were a few areas which showed evidence of new skin and healing. On the forehead, the crusts persisted for fourteen days. On the fifth day after hospitalization, he developed a mild contact dermatitis of the wrists and dorsal surface of the hands. This condition which persisted for six weeks was treated with a bland ointment. The latter dermatitis may have developed from local contact to the gas mask or to the adhesive tape, to both of which he proved to be sensitive.

\*Seen at the Allergy Clinic, Station Hospital, Camp Gordon, Georgia.

## CONTACT DERMATITIS—GILBERT

A case of repeated gas mask dermatitis is presented. This patient had definite skin reactions to gas mask rubber and the reactions coincided with those of former medical reports. A detailed report on the individual constituents of the rubber was not made because the patient was transferred to another post.

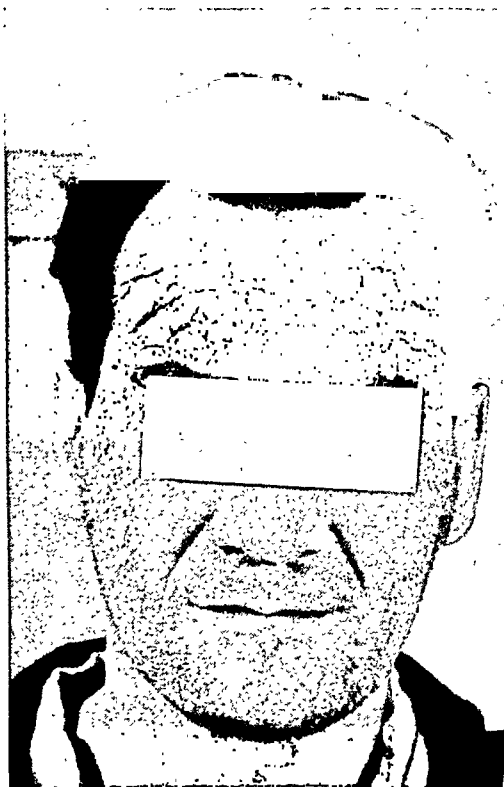


Fig. 1. Photograph taken February 16, 1943, five days after admission to the hospital. Note the marked crust formation on the peripheral portion of his face.

It was shown that these cases do not react to all process types of rubber. It is felt that the etiology may be one or more chemicals, the specific nature of which is unknown, used in processing of this rubber—probably an age resistant or anti-oxidant. This case represented an extreme sensitivity with rapid reaction to the processing materials. A different type of gas mask was ordered for this patient.

### COMENTARIO

Se presenta un caso de dermatitis que ocurrió muchas veces, debido a la goma en la máscara a gas. Este enfermo había reaccionado definitivamente a la goma en la máscara a gas, y las reacciones coincidieron con aquellas anteriormente relatadas. No se ha hecho un informe en detalle sobre los constituyentes individuales de la goma, a causa de que el enfermo fué trasladado a otro poste.

Se ha demostrado que estos casos no reaccionan a todos los tipos de goma químicamente procedidos. Parece que la etiología puede ser debida a una o más sustancias químicas, y que la naturaleza específica empleada

## CONTACT DERMATITIS—GILBERT

en el procedimiento químico de esta goma no es todavía conocida. Es probable que sea formada con el tiempo y también resistente, pudiendo ser un antioxidable. Este caso ha representado una sensibilidad extrema con una reacción rápida a los materiales químicamente procedidos. Se ha ordenado un diferente tipo de máscara a gas para este enfermo.

### REFERENCES

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2. Petro, John: Respirator dermatitis. *Brit. M. J.*, (May 23) 1942.

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### IDOSYNCRASY TO METALLIC MERCURY WITH SPECIAL REFERENCE TO AMALGAM FILLINGS IN THE TEETH. Bass, M. H.: *J. Pediat.*, 23:215, (Aug.) 1943.

Three cases of sensitivity to mercury are reported. One in a boy ten years of age who developed a rash from accidental contact with metallic mercury. A second in a girl fourteen years of age with a history of eruptions following the use of calomel at the age of four years. Later, she developed a rash from blue soap presumed to contain mercury, and at the age of seven years developed a rash from an ointment containing yellow oxide of mercury. At the ages of twelve and thirteen years, she developed an eruption on her lips and cheeks when some teeth were filled with a mercury amalgam. At the age of fourteen years, mercury amalgam fillings were again used, and a week later she developed generalized urticaria.

After three weeks without relief from various forms of therapy, the amalgam fillings were removed. This was followed by an acute exacerbation of the symptoms, but within twenty-four hours, the symptoms subsided and the child remained completely well. A passive transfer test was positive when the site was rubbed with ammoniated mercury; a control site was completely negative. A third case was a girl known to be sensitive to ammoniated mercury who developed swelling of the lips with a rash about the mouth and cheeks following an amalgam filling. The filling was not removed, and the rash disappeared two days later. The literature of the subject of idiosyncrasy to mercury in amalgam fillings is reviewed.

J. G.

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### TROPICAL EOSINOPHILIA. Emerson, Kendall: *U. S. Nav. M. Bull.*, 42:118, (Jan.) 1944.

An endemic disease, of unknown etiology, is described as being widespread in coastal regions of southern India. The clinical picture is characterized by chronic cough, weakness, weight loss, asthmatic breathing and marked leucocytosis (up to 60,000) of which eosinophiles constitute 50 to 80 per cent. The insidious onset is associated with a low-grade fever, splenic enlargement and apathy. The disease is benign, no fatalities having been reported. The diagnosis is based upon the history, the physical signs in the chest (rales and prolonged expiration), the eosinophilia, the x-ray appearance of the chest (not unlike miliary tuberculosis) and on the response to arsenical therapy. Treatment with arsenic, orally or intravenously, apparently specific, indicates the disease to be of spirochetal or protozoan etiology. Search for parasites has, so far, been unsuccessful. Complete case report emphasizes the importance of this disease in soldiers returning to this country from India.

L. J. H.



## SUBCUTANEOUS EMPHYSEMA DURING ASTHMA

NATHAN FRANCIS, M.D., F.A.C.A.

Rochester, New York

Subcutaneous emphysema complicating bronchial asthma is not common, nineteen cases being reported in the literature up to 1938. Van Fleet<sup>2</sup> and others tabulated fifteen cases and added four of their own. We now add two more cases bringing the total of reported cases to twenty-one.

Subcutaneous emphysema, sometimes called surgical emphysema, is due to air or gas in the subcutaneous areolar tissue.

The most common site of origin is in the thorax from an injured lung, rarely from the gastro-intestinal tract, or the urinary bladder after trauma. It is seen also in the presence of gas-producing bacteria such as *B. Welchii*, or *B. Coli communis*.

While the condition is seen rarely with asthma, it is seen not infrequently in other conditions.

The surgeon sees it frequently after stab wounds of the chest, broken ribs, and in the presence of gas-producing bacteria.

The nose and throat man may see it after tonsillectomy, trachiotomy or while he is inflating the eustachian tubes. Or a patient may seek his advice for sudden, unilateral swelling of the face after a sneezing spell.

The obstetrician may encounter it during difficult labor.

The pediatrician may see it during the course of measles or whooping cough.

The chest man may produce it while doing an artificial pneumothorax.

The allergist may see it rarely as a complication of an acute and prolonged asthmatic attack, two cases of which are herewith presented.

The mechanism seems to be as follows: During asthma the bronchus is plugged because of spasm, edema, and mucus. This acts as a one-way valve, allowing air to enter the alveolus, but hinders its exit during expiration. The intra-alveolar pressure is thus increased with rupture during a violent coughing spell. The free air then follows the reflexions of the pleura, pericardium, or perivascular tissues, to the posterior mediastinum, to the neck, et cetera.

All the reported cases were characterized by cyanosis, dyspnea, and swelling of the neck and adjacent parts of the body. Crepitation was a prominent feature when the area was palpated, the onset of symptoms appearing after a violent and prolonged asthmatic attack. Our two cases conform to the cases enumerated in the literature.

Multiple incisions in the suprasternal region for the relief of the emphysema has been advocated but is never indicated when the condition is due to asthma. The air is usually absorbed in about ten days.

*Case 1.*—W. L. white, male, aged thirty-one, has had bronchial asthma for the past twelve years with sensitivity and treatment for house dust. Patient was admitted to the hospital 24 hours after the onset of acute asthma. Chief symptoms were cyanosis, dyspnea, ballooning out the neck. Physical examination including x-ray studies confirmed the diagnosis of subcutaneous emphysema. X-ray check 7 days later showed that the air had been absorbed.

*Case 2.*—E. P. white, female, aged thirteen years, had attacks of bronchial asthma since childhood with multiple sensitivity including bacteria. She was admitted to the hospital with acute asthma after an acute, upper respiratory infection. She was dyspneic, cyanotic with moderate swelling at the base of the neck. Physical signs revealed subcutaneous emphysema which was confirmed by x-ray studies. X-ray check ten days later showed that the air had been completely absorbed.

From the allergy clinics of the Rochester General Hospital and Highland Hospital. Read before the staff of the Rochester General Hospital.

# SUBCUTANEOUS EMPHYSEMA—FRANCIS

## REPORTED CASES

	AUTHOR	AGE	SEX	ASTHMA	NATIONALITY
1	Watson	18	F	Childhood	Great Britain
2	Coverley	17	M	Childhood	Great Britain
3	Whitby	25	M	Childhood	Great Britain
4	Kahn	6	F	Past 6 years	U.S.A.
	MacDermot	22	M	Past 6 years	Canada
6	Schetema	30	M	1st Attack	Holland
7	Artareytia	18	M	Childhood	Uruguay
8	Kruysveldt	22	F	1 Year	Holland
9	Davidson	9	F	8 Years	British
10	Pastorino	9	F	?	Uruguay
11	Pastorino	14	M	Childhood	Uruguay
12	Shelden and Robinson	16	M	1 Year	U.S.A.
13	Kirsner	38	M	6 Years	U.S.A.
14	Dietrich	5	F	2½ Years	U.S.A.
15	Dietrich	7½	M	5 Years	U.S.A.
16	Van Fleet, Miller and Scott	10	F	2½ Years	U.S.A.
17	Van Fleet, Miller and Scott	5	M	3½ Years	U.S.A.
18	Van Fleet, Miller and Scott	28	M	21 Years	U.S.A.
19	Van Fleet, Miller and Scott	19	F	2 Years	U.S.A.
20	Francis	31	M	12 Years	U.S.A.
21	Francis	13	F	Childhood	U.S.A.

## DISCUSSION

As one looks at the reported cases it is obvious that practically all of the patients have had asthma of long duration.

The violent inspiration and prolonged and labored expiration seen in asthma causes permanent dilatation of the alveoli, if the condition persists for an extended period of time.

Microscopically, one sees great dilatation of the alveoli with marked thinning of the alveolar walls, rupture of elastic tissues, and obliteration of the capillaries.

The location in the lung where this pathologic change is most likely to occur, according to MacCallum<sup>1</sup>, is the unprotected suprathoracic apex of the lungs where the intra-alveolar pressure is capable of blowing out an alveolus under proper conditions.

## SUMMARY

1. Two cases of subcutaneous emphysema during an acute and prolonged attack of asthma are presented, thus bringing the total of this type of case reported to twenty-one.

2. While the condition is dramatic, it is never serious when associated with asthma.

3. Multiple incisions in the suprasternal region are not indicated for the relief of symptoms.

## REFERENCES

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2. Van Fleet, H. D., and Miller, H.: California & West. Med., 49:265, 268, (Oct.) 1938.

## LOCALIZED ATROPHY OF THE SUBCUTANEOUS FAT AFTER REPEATED INJECTIONS OF GRASS POLLEN

NATHAN FRANCIS, M.D., F.A.C.A.

Rochester, New York

Localized atrophy of the subcutaneous fat after repeated injections of insulin was first reported by Depisch in 1926.<sup>1</sup> The skin or the muscle in the area of atrophy was not involved in the process. This author estimated that 10 per cent of patients taking insulin were affected in this way.



Fig. 1.

Many theories have been offered to explain the disappearance of the subcutaneous fat. It is thought that the lipase in the insulin digests the fat, or that repeated injections of insulin start a low-grade inflammatory process with healing causing the atrophy by scarring. Avery<sup>1</sup> believes that the atrophy of the subcutaneous fat is a non-specific process and arises because of the repeated trauma to the penniculus adiposum.

*Case Report.*—M. A. M., white, female, aged thirty-two, was diabetic. She had been treated in our clinic for grass pollensitis since 1926. She called our attention to multiple depressed areas on the arm in which she had received most of the grass pollen injections. She stated that she had taken no insulin in the past year.

From the allergy clinic of the Rochester General Hospital.

## ATROPHY OF SUBCUTANEOUS FAT—FRANCIS

### DISCUSSION

While this condition occurs most frequently in diabetic patients at the site of the insulin injections, it may be assumed that the pollen injections had nothing to do with the above described condition. However, since the patient states that she had taken no insulin during the past year, and that the atrophy of the skin of the arm did appear while she was getting her pollen injections, it seems logical to conclude that the atrophy of the skin was associated with the pollen injections. Among the many theories offered to explain this condition, Avery believes that the subcutaneous fat atrophy is non-specific and results from the trauma to the subcutaneous fat. We feel that the condition above described, localized atrophy of the subcutaneous fat, may result, not only from injections of insulin but also from any type of injection regardless of the material injected.

### SUMMARY

A case of localized subcutaneous fat atrophy is presented which we feel was due to the injections of pollen.

### REFERENCE

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**HYPERSENSITIVITY: A NEGLECTED PHASE OF ALLERGY.** Bruck, Clifford, F.: *Mich. M. Soc.*, 42:10, (Oct.) 1943.

The author reviews the terms "Hypersensitiveness," "Allergy" and "Atopy" as well as the mode of entry of the substances with which one becomes sensitized, describing substances as nonantigenic and antigenic; the nonantigenic substances include acetyl-salicylic acid, cocaine, novocaine, and quinine. He goes into the consideration of antibodies, antigen and complement, their inter-action resulting in "Allergy." The consideration of sensitizing substances and their reactions with antibody and complement is discussed. The reticulo-endothelial system's function of phagocytosis and antibody formation is reviewed as well as the origin of these cells. The author states that "It is this sensitizing bacterial toxin or antigen liberated by a focus of infection which we are endeavoring to evaluate in this study." In their laboratory they report having developed a form of complement fixation for the detection of complement-fixing antibodies and are able to determine the antigen-producing properties. He recognizes the frank danger signal when a patient is seriously lacking in complement and surgery is avoided. Autogenous vaccines are considered in patients where the focus of infection is located beyond the reach of surgery or in patients of poor surgical risk. The best results are obtained from vaccines where primary foci of infection are found and eradicated. Vaccines made from these specific organisms are very potent and must be given in small doses. Deficient complement in the patient's blood stream indicates a bad prognosis with any form of treatment and is a definite contra-indication to surgical interference.

J.W.T.

# Editorial

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## INSTRUCTIONAL COURSE

The Committee on Education of the College, when planning its graduate continuation course in allergy, to be presented at the Coronado Hotel, St. Louis, November 4 to 8, inclusive, had certain pertinent ideas in mind.

Such courses, to be available to the greatest number of physicians, should be held just preceding largely-attended assemblies of national medical societies and at times take the place of a regional meeting of the College. Capable leaders of the various courses will be rotated when the opportunity permits and will be selected when possible, from the region in which the course is held. The present course precedes the meeting in St. Louis of the American Academy of Pediatrics, November 9 to 11, and that of the Southern Medical Association, November 13 to 16.

Since undergraduate instruction in allergy has been greatly limited in the past and only one-fourth of the medical schools in the United States give any allergy courses, the College would accomplish the greatest good, for the present at least, by teaching the practical procedures of diagnosis and treatment of the various allergic diseases. Dealing with twelve or fifteen diseases in allergy to be met in practically every specialty of medicine and general practice, it is obvious that for the majority of physicians such instruction would take the nature of an undergraduate course.

The instructors will present the practical, clinically essential features of allergy without confusing the student with controversial subjects. The material also will be of such an order that it will afford a deliberate and critical study for those advanced students of allergy wishing to refresh their knowledge of the subject. Fundamentally, it should form the nucleus for undergraduate education, training for specialization in allergy, as well as graduate training for the non-specialist.

The concentrated, accelerated curricula of premedical and medical training, resulting from war exigencies, have greatly weakened medical education. Before resuming civilian responsibilities, returning practitioners will be in need of intensive instruction in the recent developments in medical science and practice. On the other hand, many excellently-trained men, returning from the Armed Forces, will be eager to learn to recognize allergy in their practice so that they may properly refer patients to the allergy specialist or be stimulated to apply allergic procedures themselves, and such an intensive course should be very desirable. Inasmuch as the course will be given at St. Louis, which is centrally located in the Mississippi Valley, it will afford an excellent opportunity to medical officers interested in allergy, if their Command will permit them to attend. Men in the service will not be required to pay for the course.

## EDITORIAL

Experienced instructors, noted for their leadership in allergy, will conduct the courses. The beginner in allergy, desiring to become an Associate Fellow in the College, will find the course greatly to his advantage.

When presenting these courses every effort will be made to meet the approval of the Council on Medical Education and Hospitals of the American Medical Association, so that eventually there will be a Section on Allergy of the AMA.

A fairly large number of physicians took the first instructional course at Chicago last June, who were not members of the College. Both members and non-members agreed that the course was a definite success, and there has been an unusual demand for the printed abstracts of this course (perforated to fit a standard ring-book), of which there are a few complete sets available at the nominal fee of seventy-five cents per set.

Since the preliminary announcement of this second course, which appeared in the May-June, 1944, issue of the *ANNALS OF ALLERGY*, a sufficient number of men have applied to warrant the charge to be reduced to fifty dollars. Circulars will be sent to as many physicians interested in allergy in the surrounding states as possible, and advertisements will appear in a number of the leading medical journals.

As many members of the College as possible, as well as candidates and non-members, should avail themselves of this opportunity and register early. Hotel reservations should be made immediately.

All those wishing to register for this course will please communicate with Dr. French K. Hansel, President of the American College of Allergists, 634 North Grand Boulevard, St. Louis 3, Missouri.

The proposed schedule at present is as follows:

### Full-Day Classes

*Otorhinolaryngologic Allergy*—French K. Hansel, M.D., St. Louis, Missouri, with collaboration of Ralph Bowen, M.D., Houston, Texas, and Herbert J. Rinkel, M.D., Kansas City, Missouri. Botanical listings and colored slides of important pollinating offenders will be presented.

*Bronchial Asthma*—Leon Unger, M.D., Chicago, Illinois.

*Dermatologic Allergy*—Rudolf L. Baer, M.D., New York City.

*Pediatric Allergy*—Ralph Bowen, M.D., Houston, Texas, and Albert V. Stoesser, M.D., Minneapolis, Minnesota.

### Half-Day Classes

*Allergy of the Central Nervous System*—T. Wood Clarke, M.D., Utica, New York.

*Food Allergy, Including a Discussion of Gastro-intestinal Allergy*—Herbert J. Rinkel, M.D., Kansas City, Missouri.

### Evening Classes

*Drug Allergy*—Jonathan Forman, M.D., Columbus, Ohio.

*Mold Allergy*—Homer Prince, M.D., Houston, Texas.

*Physical Allergy*—Cecil Kohn, M.D., Kansas City, Missouri.

*Neurologic and Psychologic Aspects of Allergy*—Michael Zeller, M.D., Chicago, Illinois.

## EDITORIAL

*Physiologic and Immunologic Aspects of Allergy*—Fred W. Wittich, M.D., Minneapolis, Minnesota.

*Practical Demonstrations:* Skin Testing, Direct and Indirect; Other Methods of Testing; Patch Testing; Making of Extracts; Cleansing Glassware and Needles; et cetera.

F.W.W.

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### THE STANDARDIZATION COMMITTEE

When the American College of Allergists was organized, the Board of Regents realized that one of the most important problems confronting the allergist was proper methods of standardizing extracts of the various allergens. Therefore, they decided to appoint a committee whose function would be to solve this problem. A committee on Biologic Assay was designated; later this name was changed to the more precise title of Standardization Committee.

The members of the Standardization Committee, as appointed by the Board of Regents, are: Dr. George Rockwell, Chairman, with Drs. Frank Simon, H. L. Graham, Roger Wodehouse, Ethan Allan Brown, J. Warrick Thomas, F. W. Wittich, Nathan Schaeffer, George Waldbott, Willard Small, L. O. Dutton, Col. S. W. French, and Major Lawrence Halpin. At the recent meeting of the College, the Standardization Committee voted to form a Council which would act and decide on all matters concerning the Committee. This Council is composed of George Rockwell, Chairman, and Drs. F. W. Wittich and J. Warrick Thomas.

To determine a satisfactory method of standardization is not an easy task. It requires much original research with very careful checking of every possibility. However, the value and importance of the work of this committee cannot be overemphasized, since the development of a uniform standard for extracts will be a great step forward in allergy.

G.E.R.

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### MICROFILM OF ARMY MEDICAL LITERATURE READILY AVAILABLE†

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†Spanish translation appears on Page xii.

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to be presented by

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form standard for extracts will be a great step forward.

# Progress in Allergy

Under the direction of ETHAN ALLAN BROWN

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## IMMUNOLOGY IN 1943

A. J. WEIL, M.D., F.A.C.A.

Pearl River, N. Y.

Immunology is a branch of physiology in its own right, but its aspects and applications extend deeply into various fields of physiology and pathology. Some of those are related to the problems that occupy the allergist, others are not likely to enter the circle of interest of our specialty. It is not easy to draw a distinguishing line between what will be of importance to allergists.

An enumeration of the more important accretions in factual knowledge during 1943 has been attempted. Within the limits imposed by the space available for such an enterprise the account cannot possibly be complete. Papers have been preferred in the bibliography that will, besides reporting new facts, serve giving access to the literature on a given problem, and it has also been attempted to make the reader familiar with the general trend of thought on immunological problems.

A new textbook of immunology by Boyd<sup>12</sup> has many excellent features. Its value as an introduction into the field is somewhat limited by uneven presentation and lacunary and sometimes incorrect data.

*The Journal of Immunology* has extended its scope to publication of selected reviews. Volume 46 contains a progress report on bacillary dysentery<sup>173</sup> and one on *Salmonella*.<sup>11</sup> Volume 47 offers a valuable report on the techniques and results of immunochemistry<sup>83</sup> which ought to be of great assistance to those interested in the theoretical aspects of our field as well as to those concerned with the critical evaluation of experimental technique.

A useful report on laboratory methods for the diagnosis of virus diseases will be found in *The Journal of the American Medical Association*.<sup>166</sup>

The theory of immune precipitation has been reviewed by Pauling.<sup>125</sup> There is little doubt that Ehrlich's "lock and key" theory of the relations of antibody to antigen is fundamentally correct if adapted to modern concepts of chemistry. What is still controversial to a certain degree is the question of how the primary antigen-antibody complexes proceed to aggregate. There are two theories concerning this matter. The first one explains aggregation as an unspecific process. The case is vividly presented in Boyd's book.<sup>12</sup> According to the second theory, the formation of visible precipitates is achieved by alternate linkage of the primary complexes of antibody and antigen. A simple consideration shows that this can occur only if both antigen and antibody are multivalent, that is, if either has more than one point of combination. The multivalence of antigen is undisputed. The current controversy is concerned with the valency of antibodies, and, in this respect, the year 1943 has brought forward several papers that provide additional evidence that antibody is indeed at least bivalent.<sup>72,126,135</sup> Bond strength,<sup>135</sup> quantitative relations,<sup>117</sup> rate of combination,<sup>74</sup> its reversibility<sup>73</sup> and the Danysz phenomenon<sup>75</sup> were discussed on the basis of new experimental data.

Pauling's working hypothesis according to which the specificity of antibodies is explained by the manner in which the various amino acid groupings of globulin are folded up, so that groupings particularly adapted to the combining group of antigen come to the surface of the molecules, has led to a revival of attempts to produce artificial antibody by exposing non-antibody globulin to antigen under conditions expected to facilitate rearrangement of the molecules.<sup>4</sup> These experiments

have roused an understandable public interest. But before claims in this direction can be recognized, more solid experimental evidence is needed. At the present, the criticism of Kabat<sup>83</sup> appears to be fully justified.

The relation of "iodo" specificity to the degree of iodization of a given protein was studied,<sup>153</sup> and in agreement with prior observations, found to parallel the amount of iodine combined with the protein.

A method was devised<sup>113</sup> that utilizes the immunological specificity of Bence-Jones protein for the quantitative assay of this protein in serum.

In connection with attempts to find a substitute for human plasma for transfusion, a partial loss of antigenicity was found to be obtainable by treatment of serum proteins with urea or guanidine<sup>40,41,137,101</sup> and also with alkali.<sup>31</sup> This loss of antigenicity does not parallel changes in specificity—which is another example of the fact that antigenicity and specificity are not necessarily conditioned by the same configuration.

The formation of albumin-globulin complexes by heating (that had been shown to influence deeply immune precipitation) was found to be conditioned by the presence or absence of salt ions.<sup>85</sup>

Treatment with guanidine does not destroy the antibody activity of a rabbit pneumococcal serum though it did influence the combining ratio of the reaction<sup>41</sup>—as had been found before for acid-treated rabbit antibody.

The isohemagglutinins from human sera were found<sup>132</sup> to be precipitated without impairment by 25 per cent methanol—which procedure provides a convenient method for the concentration of these antibodies.

By the administration of isotopic amino acids (containing  $N_{15}$ ), it has been shown<sup>149,150</sup> that amino acid replacement and nitrogen transfer among individual amino acids occur in antibody—as in normal serum proteins—in the same manner as in organ-proteins. By the rate of disappearance of  $N_{15}$  from antibody, it was possible to estimate the half life of antibody molecules as being around two weeks, which is approximately the same as that of serum protein. Passively introduced antibody does not participate in the N replacement<sup>69</sup>; that means that this antibody—even though derived from the same species—remains "foreign." (These results were published in 1942 but they are too important to be omitted here.)

Data<sup>156</sup> on the optimal conditions for production of sperm iso-agglutinin in mice illustrate the dependence on dose, route of injection and period of immunization for production of an antibody response to material of low antigenicity.

Histamine-protein complexes are antigenic, and animals immunized with such histamine complexes are protected against anaphylactic shock to some degree.<sup>49</sup> The protection against shock can be passively transferred. The same histamine compound was found<sup>25</sup> to elicit antibody response in man. Whether such sera of human origin have histamine neutralizing power is not quite certain.

Differences in the antigenic make up of individual human sera were observed.<sup>28</sup> Evidence of such differences was obtained by cross-absorptive tests. This investigation opens a field of exploration of great interest to the geneticist.<sup>29</sup> Their possible bearing on the explanation of transfusion reactions also merits further attention.

A spectrophotometric method of antibody-N determination was described.<sup>70</sup> It allows assay of 10  $\mu$ g of antibody-N with a possible error of  $\pm 2$   $\mu$ g. This method is particularly useful when only a small amount of antibody is present as exemplified in the determination of the antibody response in pneumococcal pneumonia.

Experiences<sup>105</sup> with human serum—stored in vacuum dried form—for the prophylaxis of measles, scarlet fever, whooping cough, mumps and chicken pox and in the treatment of scarlet fever and whooping cough are most encouraging. The only exception in this respect is the experience with chickenpox. In this study, which covers a period of eight years, both convalescent and normal serum were used for

measles, mumps, chickenpox and scarlet fever, reconvalescent serum for scarlet fever and hyperimmune serum for whooping cough.

Research in the field of blood groups and blood types has concentrated particularly on the Rh factors.<sup>54,176,177,185</sup> Details of these theoretically and practically equally important investigations have to be looked up at the proper places. The technique of blood-group determination for transfusion as recommended by the British medical services, has been published in pamphlet form.<sup>184</sup>

The functional interrelation of carbohydrates has been emphasized by Morgan's observations<sup>115,116</sup> that the antigen specific for blood group A combines with the proteic compound of the somatic antigen of the *Sh. shigae* in the same manner as do bacterial haptens and these complexes are likewise highly antigenic.

Mouse tissues contain an antigen related but not identical with the classical Forssman antigen.<sup>17</sup>

Antibodies against a brain-specific antigen were obtained<sup>80</sup> in rhesus monkeys by immunization with a mixture of alcoholic brain extract + a protein conveyer + a vaccine made from tubercle bacilli + aquaphor + paraffin oil. The significance of this observation is seen in the fact that antibodies of "Wassermann type" have for the first time been obtained experimentally in animals other than rabbits.

Injection of anti-placenta serum into pregnant rats was found<sup>151</sup> to lead to fetal death by degeneration of the placenta. The same antibody causes a chronic progressive nephritis—independent of the sex of the animal—and anti-kidney sera have the same effect. There are at the present time only preliminary reports available on these investigations but it is obvious that they merit the attention of the allergist.

Indications as to the sites of antibody-formation were obtained<sup>32</sup> in experiments on rabbits injected with pneumococci or streptococci; tissue extracts of such animals were serially compared with circulating antibody level. In this way antibody was found earlier in the local site of injection and also in organs known to fix antigens (liver, spleen and bone marrow) than in the blood.

Even though it goes to somewhat beyond the limits of this review, it is worth while to mention some recent results in the investigation of the nature of inflammation because they cannot fail to influence thought on immunity and allergic phenomena. Three factors have been isolated<sup>108,109,110</sup> which regulate the development of inflammation; leukotaxine which promotes the immigration of leukocytes, increased capillary permeability and fibrinous thrombosis; a leukocytosis—promoting factor; and most recently necrosin which engenders lymphatic blockade and necrosis, and which also appears to incite fever. The pH of the inflamed area regulates the type of phagocytes in the inflamed area.

Increase of extracellular fluid is a factor counteracting the spread of infection and estrogenic hormone is effective in this respect.<sup>167</sup>

Protein depletion—for instance, by experimental starvation—affects unfavorably the capacity of antibody-production (agglutinins), particularly in young animals.<sup>20</sup> Phagocytic activity is also deeply influenced by the protein-balance.<sup>27</sup>

The blockading effect of inflammation explains, according to recent investigations,<sup>52</sup> the lack of therapeutic effect of antitoxin administered late in the disease; as long as no "fixation" by blockade has taken place, the exudate is rich in antitoxin and its reabsorption slow because of inadequacy of lymphatic drainage. Once access to the inflamed area is blocked, it cannot be reached by antitoxin.

How complicated the equilibrium is that dominates the cellular defense mechanism, was demonstrated<sup>27</sup> by observations according to which temperature and insufficiency of a number of vitamins of the water-soluble group, as well as ascorbic acid, are additional important influences.

Rabbits that had been made leukopenic by benzene poisoning acquire<sup>148</sup> fatal streptococcic septicemia after intracutaneous infection with strains which in normal rabbits cause only local infection. This is explainable by the absence of local phago-

cytic reaction; however, other "exudative" processes which normally contribute to localization of infection are also more or less paralyzed by the poison. Presence of antibody, actively acquired or passively introduced, partially neutralizes this effect. Thus, it is shown that antibody provides an additional and to a certain degree independent mechanism of fixation of an infective agent.

A quite parallel effect of alcohol poisoning and its counteraction by antibody was demonstrated for the case of pneumococcal infection.<sup>99</sup>

Evidence has been given<sup>61,62</sup> that inherited resistance to mouse typhoid in mice parallels their ability to mobilize their leukocytic defense mechanism.

Hyaluronidase counteracts "walling-off" activity insofar as it favors the spreading of an infecting agent in the tissues.<sup>111</sup> Better methods for the estimation of hyaluronidase have been devised and advantage has been taken of sensitive methods of its detection for the early diagnosis of gas gangrene in wounds.<sup>103,104</sup>

A similar diagnostic use has been proposed for lecithinase of *Cl. welchii* which is identical with the alpha toxin.<sup>103,104</sup>

It has also been proposed<sup>130</sup> to use specific antihyaluronidase or antitoxic sera for the quick presumptive diagnosis of the causative agent of wound infection.

Even though highly specific antihyaluronidases have been found in antibacterial sera, the isolated enzyme has been found to be not only nonantigenic but not even to possess hapten quality.<sup>87</sup>

Two more examples have been given for the enhancing effect of adsorption of antigens on corpuscular elements as, for instance, aluminium hydroxide on antigenicity.<sup>78,136</sup>

The gains in sensitivity of *in vitro* testing with the collodion-particle technique was stressed in several papers.<sup>19,97</sup>

The ability of the guinea pig to produce plentiful precipitin was confirmed<sup>178</sup> in a study of anti-hemocyanins from guinea pigs and rabbits which brought out the similarities and dissimilarities of the antibodies of the two species.

A contribution to the question of autosensitization was made in experiments<sup>68</sup> in which precipitins against lapine skin autolysates were obtained if—and only if—the rabbits received simultaneously but at different sites injections of a staphylococcal filtrate. The authors use the term "synergistic action" to explain this effect, but it need hardly be stressed that this term is no substitute for an adequate understanding of the phenomenon. Repetition of these interesting experiments would be desirable for more than one reason.

Cold agglutinins were found in a case of gangrene of the finger tips to the enormous amount of 1.5 mg. antibody N/ml.—which is in the order of 10 per cent of the total serum protein.<sup>158</sup> A hemolytic effect of such antibody was observed after shaking.<sup>159</sup>

The C protein—which occurs during the acute state of several infections and which precipitates pneumococcal C carbohydrates—is an alpha globulin and thus distinguished from the ordinary C antibody which is a gamma globulin.<sup>127</sup>

Human complement has been extensively studied. For details reference has to be made to the original papers.<sup>33,34,35</sup> San Clemente and Ecker gave a method of estimation of the third component of complement.<sup>145</sup>

There is another report<sup>88</sup> denying that there is a correlation between complement and vitamin C.

The fundamental data of Heidelberger and his associates on complement and its estimation by N determination found another confirmation.<sup>65</sup> It was shown that prior findings on the ratios of combination and other quantitative elements of complement fixation are applicable also for the case of *Brucella* antigen-antibody systems.<sup>133,134</sup>

The ratios and time and temperature factors of pneumococcal S-anti-S complement fixation reaction have been given a careful analysis.<sup>139,140</sup> The effect of tem-

perature on complement fixation gives indication of an as yet unknown inhibiting factor in serum that influences the rate of fixation.<sup>67</sup>

The second complement component was found to be lacking in mice.<sup>16</sup>

Enzyme solutions from *Leuconostoc mesenteroides* have the capacity of synthesizing serologically active polysaccharides from sucrose; it was found that such enzymes act type-specifically, that is, they synthesize polysaccharides exactly similar to the one of the type from which the enzyme is derived.<sup>71</sup>

Salicylate has an inhibiting effect on immune precipitation that is probably due to an interaction of this anion with the antibody.<sup>24</sup>

Colon bacilli can cause unspecific agglutination of erythrocytes and other corpuscular material<sup>148</sup>—a fact worth mentioning as a possible source of nonspecific reactions.

We restrict ourselves to providing a list of references on bacterial and virus immunology sufficient to give access to recent data for those who might become interested in the one or other special problem. Bacterial allergy is a field in which many desirable details of information are still lacking. Papers on this subject do not always give due consideration to the complicated specificities of microorganisms. On the other hand, very little is known as to whether the antigens that dominate immunity, and that, therefore, stay in the foreground of the interest of the bacteriologist, are necessarily also important as allergic antigens.

**Bacteria.**—*Enterobacteriaceae*<sup>3,10,11,14,36,37,47,48,51,77,86,95,96,114,146,152,162,163,164,172</sup>; *cholera bacillus*<sup>55</sup>; *streptococci*<sup>88,91</sup>; *staphylococci*<sup>60</sup>; *pneumococci*<sup>18,118,121,122,183</sup>; *neisseria*<sup>15,131</sup>; *H. influenzae*<sup>1,2,121,122,183</sup>; *H. pertussis*<sup>8,50,112,155,175</sup>; *clostridia*<sup>130</sup> (see also under gas gangrene toxin; *leptospira icterohemorrhagiae*<sup>92</sup>; *trypanosomes*<sup>30</sup>; *rickettsiae*.<sup>138</sup>

A peculiar hemorrhagic effect of certain bacteria, particularly of gram-negative rods on mice tumors, has been studied in considerable detail.<sup>82,179-182</sup> A similar effect has been described in the placenta where such bacterial material leads to hemorrhage and fetal death. A degree of immune protection can be obtained which surprisingly has turned out to be largely nonspecific. We mention these investigations because they might possibly turn out to be of considerable interest for the understanding of bacterial infection and its relations to hypersensitivity reactions. For the time being nothing certain is known about its mechanism and still less about the substance engendering it. The term endotoxin employed by the investigators explains nothing and it apt to create confusion because it is commonly used as synonym with somatic antigen. And it is not certain that the somatic antigen is also the carrier of the hemorrhagic effect.

Of particular interest is a report concerning the separation of the Forssman antigen from the C antigen of pneumococci.<sup>57</sup> The two substances are in many respects similar, and it appears likely that the Forssman antigen is distinguished by a lipid-like compound that enters into a complex formation with the carbohydrate. The complicated chemical relations are paralleled by the complex antibody response upon the introduction of such antigens.<sup>58</sup> Thus, the following antibodies were found to be evoked by injection by R pneumococci—that, is the rough variant devoid of the type specific S substance; (1) against the C carbohydrate, (2) against the Forssman carbohydrate; (3) against the lipid part of the Forssman antigen; (4) an agglutinating antibody unrelated to either of those antigens.

**Bacterial Toxins, Antitoxins and Toxoids.**—Tetana<sup>13,26,43,59,77,119,120,128</sup>; diphtheria<sup>9</sup>; *staphylococcic*<sup>42,46,60</sup>; gas gangrene.<sup>44,45,100,106,142,160,161</sup>

From several independent investigations—two of which were published during 1943<sup>141,157</sup>—it appears now to be certain that pertussis bacilli produce a toxic factor different from the "bacterial" agglutinin—characterized by its lability, its necrotizing effect in the skin of rabbits and its toxicity in mice. This factor is antigenic and the antibody neutralizes the toxic effect. The toxic factor can be detoxified with-

out losing its antigenicity. The role of this toxic factor in human infection is still uncertain.

*Viruses.*—Vaccinia<sup>7,154</sup>; mumps<sup>30</sup>; complement fixation test in virus diseases 6,21,22,30,53,63,64,66,70,87,94,123,170; lymphogranuloma venereum<sup>63,64,93,94,123</sup>; hemagglutination by viruses<sup>23,76,98</sup>; active immunization with measles<sup>165</sup>, and encephalitic virus.<sup>124,144,147</sup>

In primary atypical pneumonia, so prevalent during 1943, a cold agglutinin is formed with remarkable frequency,<sup>107,120,171</sup> and, in addition, an antibody that is indicated by agglutination of certain strains of streptococci.<sup>168,169</sup> Antibody-formation of this type has been described in quite a number of diseases—see, for instance, mononucleosis—: they pose a question that should be of considerable interest to the allergist. It is quite possible that they present examples of heterophile reactions entirely or partially directed against (pathological) substances originating from the host's body. (In this group also the Wassermann reaction has to be included.)

Concerning anaphylaxis only a few points pertaining to the more general aspects of this phenomenon can be mentioned at this time:

Contraction of the iris in anaphylactic shock is independent of the parasympathic innervation.<sup>5</sup> It is suggested that the miotic effect is probably not connected with liberation of histamine nor with that of acetylcholine.

Experiments indicating a role of complement in the production of anaphylactic response of isolated tissue merit further attention.<sup>98</sup>

A passively transferrable antibody has been found<sup>84</sup> in serum sickness which is obviously independent of the precipitating antibody.

Signs of supersensitiveness were observed<sup>56</sup> in rabbits treated with vaccinia virus. This is, as far as the author is aware, the only observation on virus as a sensitizing agent and they fit well with older observations.<sup>174</sup> Vaccinia virus is found in quite sizable amounts in vaccinal lesions. Further investigation of the supersensitivity to viruses might conceivably open a hitherto entirely neglected field.

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# News Items

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## THE SEVENTH ANNUAL FORUM ON ALLERGY

The Seventh Annual Forum on Allergy will be held in Pittsburgh at the Hotel William Penn on Saturday and Sunday, January 20 and 21, 1945. The program promises to excel in outstanding instructors and subjects. For those who arrive early, the Pittsburgh Committee will offer an interesting clinical program Friday afternoon and Friday evening. The American Association of Allergists for Mycological Investigations will hold its Annual Program in connection with the Forum as it did in St. Louis last year.

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## THE ASTHMA AND HAY-FEVER FOUNDATION

The Asthma and Hay-Fever Foundation was incorporated as an organization, without profit, in Ohio, 1931. During the following years it has served a useful purpose in raising money for research. Last year it was reorganized to develop and support a more comprehensive program of research and education. It functions chiefly through grants-in-aid when the proper application has been approved by a scientific advisory committee. The Corporation is under the control of the Board of Trustees who determine its administration and establish its policies. Contributions are welcome from anybody interested in the advancement of allergy. Address all inquiries and send all contributions to: Jonathan Forman, M.D., Executive Secretary, 956 Bryden Road, Columbus 5, Ohio.

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## CHEST SPECIALISTS PROPOSE TO UNITE

At their annual meeting in Chicago, June 10, the Board of Regents of the American College of Chest Physicians adopted a proposed plan for establishing a Board for Diseases of the Chest. This was introduced by Dr. J. A. Myers, Minneapolis, chairman of the committee appointed last year to study the advisability of establishing such a board. It was proposed that the following organizations be invited to meet with a committee of the College to study plans and urge the establishing of a Board of Diseases of the Chest as an integral part of the present Board for Medical Specialities, namely: American Heart Association, American Association for Thoracic Surgery, American Broncho-Esophagological Association and American Trudeau Society. Should the societies mentioned agree to join with the American College of Chest Physicians to establish a board for the speciality of diseases of the chest, steps should then be taken to incorporate this board into an independent body in accordance with the provisions established by the Advisory Board for Medical Societies, and as published in their official bulletin. Application should then be made in the proper manner to the Advisory Board for Medical Specialities for membership on the Board of Medical Specialities.

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## COL. SANFORD W. FRENCH II RETIRES

The July 29 issue of the *Journal of the American Medical Association* carried the following announcement concerning the retirement of Col. Sanford W. French II:

"Special orders were issued recently from the headquarters of the Fourth Service Command announcing that Col. Robert C. McDonald, commanding officer of the England General Hospital, Atlantic City, is replacing Col. Sanford W. French II as Fourth Service Command surgeon. Colonel French, who has been command surgeon for the past two and a half years, is on sick leave from the Lawson General Hospital. His retirement will end a military career of forty-two years' continuous service, eight years as chief petty officer in the Navy with service in

Guam and the Philippine Islands and thirty-four years in the Army with service in Panama and at ten different posts within the United States.

"In addition to heading the medical branch, Headquarters Fourth Service Command, Colonel French was the instigator of establishing eighty-nine allergy clinics in 1942 at general and station hospitals throughout the command. Another project which Colonel French was instrumental in establishing is the treatment of acute venereal diseases while patients are kept on a duty status. This project was pioneered in the Fourth Service Command in March, 1942, but after a War Department report in 1943 it was made standard operating procedure for all service commands. The most recent program with which Colonel French has been affiliated is the reconditioning service for wounded men returning from overseas. Two years ago a small reconditioning service was set up in station hospitals, but it was not until recently that the need for a definite program was recognized by the Surgeon General's Office in Washington. The Daytona Beach Convalescent Hospital, under command of Col. Philip L. Cook, is the latest Fourth Service Command installation giving full time to this new reconditioning program. Following his retirement, Colonel and Mrs. French will live in San Antonio, Texas."

Colonel French, who is an Honorary Fellow of the College, and Major Lawrence J. Halpin, a member of the Board of Regents of the College, presented a paper entitled "Allergy in the Army," June 10, 1944, at its first annual meeting. It was the first report of accurate mass statistics concerning the incidence and results of therapy of allergic diseases in the Armed Forces of the United States. This has been discussed in an editorial in the May-June, 1944, issue of the *ANNALS OF ALLERGY*. Included in the report by Colonel French and Major Halpin was the successful treatment of 6,842 patients with poison ivy; 8,139 patients were hospitalized on account of their allergies with a loss of 172,455 days in the hospital. It is estimated that in this single Service Command the valuable services of 20,000 men were saved for the Army. By making allergenic extracts at their central laboratory, there was an enormous financial saving compared with the commercial method of supply. Millions of dollars are spent each year in the control of venereal disease and yet last year there were more cases of clinical allergy of disabling severity (hay fever and asthma) than there were of venereal disease in their Command.

#### VETERINARY SECTION OF THE AMERICAN COLLEGE OF ALLERGISTS

Dr. I. Forest Huddleson, of the Central Brucella Station of the Division of Veterinary Science, Michigan State College of Agriculture and Applied Science, East Lansing, Michigan, was appointed temporary chairman of the Veterinary Section on Allergy of the American Veterinary Medical Association, following an organization meeting of the proposed Section on Veterinary Allergists, June 9, 1944, at Chicago, preceding the first annual meeting of the College. This meeting was arranged by officers of the American Veterinary Medical Association and the American College of Allergists. Dr. J. C. Hardenbergh, Executive Secretary of the American Veterinary Medical Association, was present at this meeting. Doctor Huddleson will prepare a report of this joint conference and will present it to the Executive Board of the American Veterinary Medical Association at its eighty-first annual session at the Palmer House, Chicago, August 22 to 24, 1944, inclusive. Doctor Huddleson proposes to recommend that the American Veterinary Medical Association consider the formation of a new section within the association and to be designated as "Veterinary Section of the American College of Allergists"; further, that the Veterinary Section be given a place on the program of each annual meeting of the American Veterinary Medical Association. The Board of Regents of the American College of Allergists has voted to accept a limited number of outstanding contributors to veterinary allergy as Active Fellows in the College. It is proposed that the men be selected for Fellowship by a committee appointed by the American Veterinary Medical Association and approved by a two-thirds majority vote of the Board of Regents of the College. Whether they will be made

## NEWS ITEMS

Associate or Active Fellows after they apply will depend on the recommendation of the American Veterinary Medical Association's Membership Committee and the decision of the Board of Regents of the College.

### FIRST ANNUAL MEETING OF THE AMERICAN ACADEMY OF ALLERGY

The first annual meeting of the American Academy of Allergy will be held in New York City, at the Waldorf-Astoria, December 11 and 12, 1944. Members of the College, who are members of the Academy as well as all other members of the College, are urged to be present and to make their hotel reservations early.

### J. WARRICK THOMAS TO BE ASSOCIATED WITH VAUGHAN MEMORIAL CLINIC

Dr. J. Warrick Thomas, head of the Department of Allergy at the Cleveland Clinic since January 1, 1939, is to be associated with Dr. W. Randolph Graham in the establishment of the Vaughan Memorial Clinic, 201 West Franklin Street, Richmond, Virginia. Dr. Thomas received his speciality training in allergy under the tutelage of the late Dr. Warren T. Vaughan, following the completion of his internship and medical residency at the University Hospital of the University of Georgia School of Medicine. He is a member of the Board of Regents of the American College of Allergists, a member of the American Academy of Allergy, and is well known in allergy circles. He is perhaps best known for his work in editing "Allergy in Clinical Practice," published in collaboration with other members of the staff while head of the Department of Allergy at the Cleveland Clinic.

Dr. H. Harold Gelfand announces the removal of his office to 20 Park Avenue, New York City.

Dr. Samuel J. Levin, Lieutenant Commander, Medical Corps, United States Naval Reserve, announces his return from active duty. Doctor Levin has opened offices at 469 Fisher Building, Detroit, Michigan, and is limiting his practice to allergy.

### INSTRUCTIONAL COURSES AVAILABLE

Sets of the complete instructional courses presented at the First Annual Meeting of the American College of Allergists in Chicago, Illinois, June 10 and 11, 1944, are available at the nominal charge of 75 cents a set.

Subjects and authors are listed below:

- The Eczematoid Dermatoses of Infants and Children—JEROME GLASER, M.D., F.A.C.A., Rochester, N. Y.; CHARLES S. MILLER, M.D., Corona, N. Y.
- The Diagnosis and Treatment of Allergy of the Nose and Paranasal Sinuses—FRENCH K. HANSEL, M.D., F.A.C.A., St. Louis, Mo.
- Gastro-Intestinal Allergy—ORVAL R. WITHERS, M.D., F.A.C.A., Kansas City, Mo.
- Allergy of the Central Nervous System—T. WOOD CLARKE, M.D., F.A.C.A., Utica, N. Y.
- Allergic Migraine—J. WARRICK THOMAS, M.D., F.A.C.A., Cleveland, Ohio.
- Dermatologic Problems in Allergy—LOUIS A. BRUNSTING, M.D., F.A.C.A., Rochester, Minn.
- Bronchial Asthma—LEON UNGER, M.D., F.A.C.A., Chicago, Illinois.
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# BOOK REVIEWS

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POLLINOSIS (Hay Fever). By Leopold Herraiz Ballesterro, M.D., and Juan Victor Monticelli, M.D. 227 pages. Buenos Aires: Libreria Hachette, 1943.

This book is a review of the problem of pollinosis in the provinces of Buenos Aires, Santa Fé, Cordoba, San Luis, Mendoza, and in the Pampa (the extensive plain), Neuquen and Rio Negro. It is divided into two parts, each part being subdivided into five chapters respectively.

Part I is concerned with botanical studies, pollen counts, studies of cutaneous reactions, et cetera.

In the first chapter the authors go into detail of the regional botanical data which are indispensable for the diagnosis and treatment of pollinosis. The classification of the anemophylous plants is extremely well described.

In the second chapter the anemophylous flora of the Republic of Argentine are considered. The national botanical studies made by Thommen, Jimenez Dias, Balyeat, Schepegrell, Leeuwen and Guttman, Sanchez Cuencas, Vaughan, Rowe, Wodehouse, Gonzales, Shahon, Pova, and several others are mentioned. The personal studies made by the authors on the Argentine flora are also very well brought out.

The third chapter is devoted principally to the atmospheric pollen count and studies in the Federal Capital and its surrounding suburban towns and villages, Bahia Blanca, Fortin Mercedes and Santa Rosa. It contains also four excellent tables of the chronology of pollination.

The fourth chapter deals principally with the study made on patients, namely the seasons of the persistence of the symptoms, the responsible species, the studies made on cutaneous reactions, and the authors' personal studies.

The fifth chapter deals with the conclusions which permitted these authors to bring out their studies and experiences. They emphasize the fact that the physicians who expect to treat pollinosis must know thoroughly these four points: (1) The dispersion of each species and the floral map; (2) the intensity of pollination; (3) the activity of the pollen; and (4) the chronology of pollination. This chapter is enriched with a five-page floral calendar.

Part II deals mostly with the clinical aspect of pollinosis.

The first chapter deals with the definition and the pathological physiology of the reverses or disturbances which determine pollinosis. The authors state that 60 per cent of the cases with a positive family history of allergy developed the disease before the 25th year, and 83 per cent before the thirtieth year. Forty per cent of those cases with a negative family history of allergy developed the disease before the twenty-fifth year, and 60 per cent before the thirtieth year.

The second chapter deals with the diagnosis of pollinosis. Here methods of testing are discussed and the necessary armamentarium for testing is enumerated.

The third chapter deals with the treatment of pollinosis. The authors bring out the importance of elimination when this is practicable. The method of specific desensitization or immunization is very well discussed and described.

The fourth chapter deals with the nonspecific treatment of pollinosis. This treatment seems to be of value in about 5 per cent of the cases, and consists in taking the following measures: (1) Dietary measures, the diet being principally of vegetables, because of their low salt, protein and purin content; and (2) oral and parenteral therapy.

The fifth chapter describes the regional characteristics of pollinosis. These authors bring out the fact that the pollen content of the city is much less than that of the country and suburbs.

The preface written by Carlos Jimenez Dias depicts the excellent accomplishment

of Doctor Ballesterro whom he addresses by the familiar name of Herraiz, in his early days as a student in the Faculty of Madrid, Spain. He states that the authors of this work on pollinosis have efficiently studied the botanical flora of the Republic of Argentine and besides have pointed out other plants whose pollens were not known to cause pollinosis until now. He concludes by saying that this is the first publication of its kind which, he hopes, will continue to be a symbol of further research and benefit to all sufferers of pollinosis and other allergic manifestations.

The impression of the reviewer is that this book is a complete presentation of the subject of pollinosis in the Republic of Argentine. Every chapter reflects the extensive experience and studies of these authors in this most important field. This book is of value to the general practitioner and the specialist as well. It represents a product of much research and great personal interest in pollinosis. H. I. S.

**ELIMINATION DIETS AND THE PATIENT'S ALLERGIES: A HANDBOOK OF ALLERGY.** By Albert H. Rowe, M.D., Consultant in Allergic Diseases, Alameda County Hospital, Oakland, California. Second edition. Cloth. Price, \$3.50. 256 pages. Philadelphia: Lea & Febiger, 1944.

The second edition has a larger type page to enable an expansion of the text as a result of accumulation of new material, without increasing the number of pages. There are five chapters, including an appendix. As a handbook, stressing food allergy, the author has admirably succeeded in accomplishing his purpose. Nearly the entire first half of the book is devoted to a brief discussion of the value of elimination diets compared to skin tests with foods, the diagnosis, causes and the control of clinical allergy. This part of the book in its brevity is no doubt intended to emphasize those principles requiring collateral reading by the beginner in allergy.

The second half of the book displays the ability of the author, who has been a pioneer in food allergy, when presenting many useful, revised elimination diets for the determination of food allergy. These revised diets are so varied that it makes it comparatively easy to furnish an adequate diet with the exclusion of offenders to apply to almost every patient sensitive to various foods. Supplementing these suggested menus are many useful and practical recipes. It is a storehouse of valuable information, also, regarding the various components in the preparation of a variety of foods. The ingredients of various baby foods, beverages, bread stuffs, confections, canned goods, cereals, commercial preparations of all kinds of meat products, seasonings, et cetera, are listed in detail. In addition, there is a discussion of the various vitamins when arranging an elimination diet. Considering the difficulty when arranging such detailed information, this part of the book is very well organized. In view of the observations of Coca on familial nonreaginic food allergy, the importance of the role of foods in allergic diseases has increased. Any physician who is interested in the subject of allergy should not be without the book, and the general practitioner who does not do skin tests will find the manual very useful.

F. W. W.

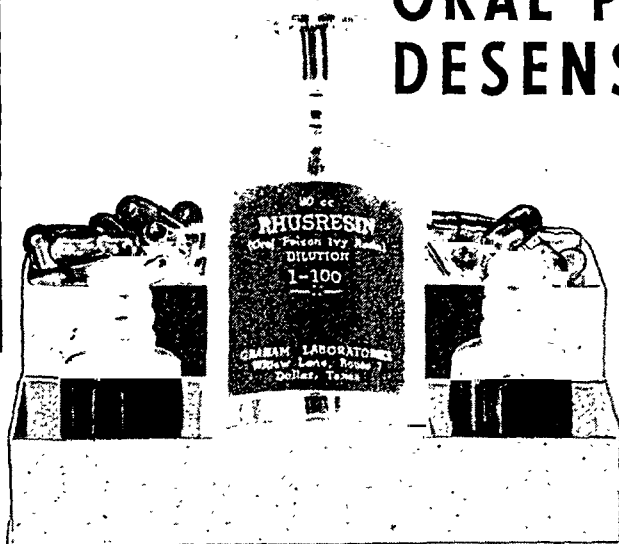
**SECRETORY MECHANISM OF THE DIGESTIVE GLANDS.** By B. P. Babkin, M.D. 900 pages. 220 illustrations. Price \$12.75. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper and Brothers, 1944.

The author, a scientist of international reputation in investigative physiology, has very successfully organized his course of lectures describing the various mechanisms involved in the regulation of the secretory activity of the principal digestive glands. Although not a monograph, it serves as a physiological introduction to the pathology and the clinical study of the secretory apparatus of the gastrointestinal tract. The author indicates that the importance of furthering our knowledge of these important mechanisms depends upon combining physiological inves-

*(Continued on Page xii)*



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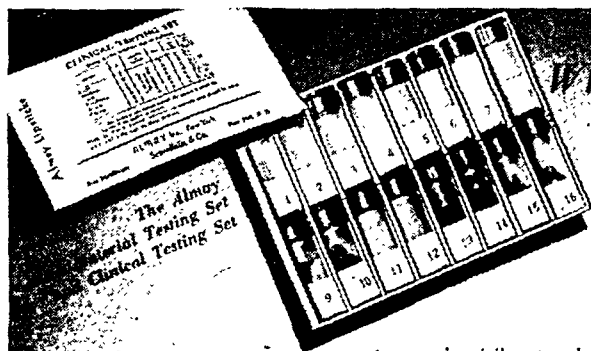
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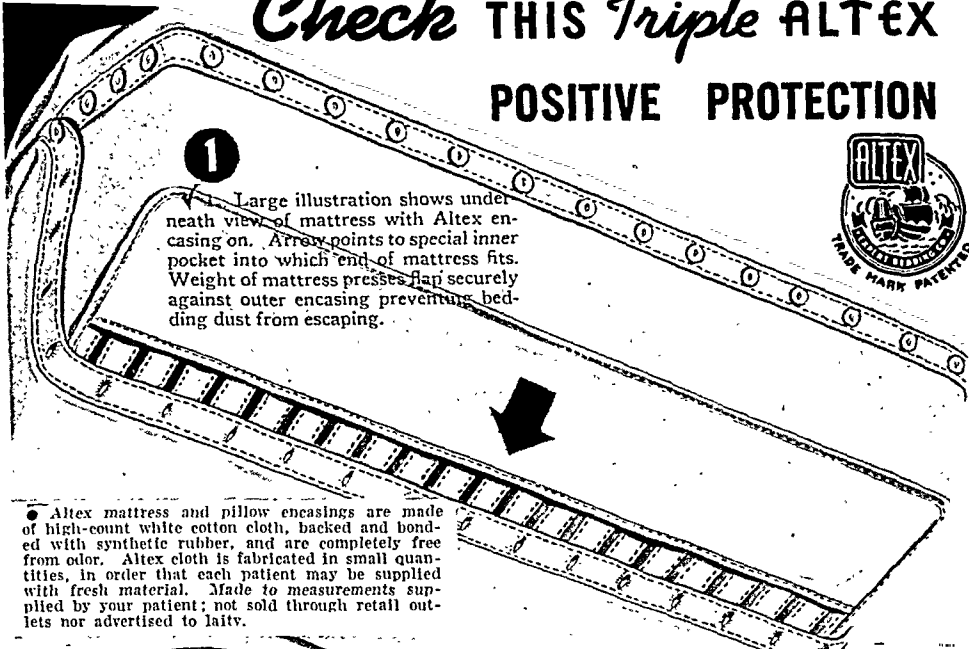
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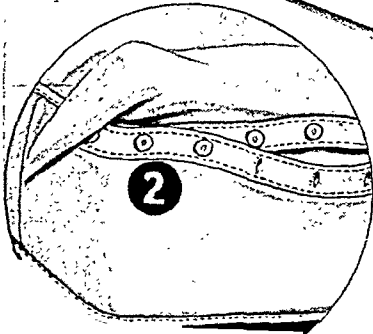


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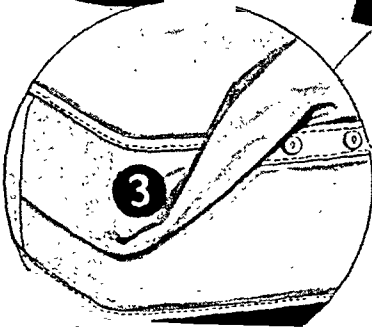
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(Spanish translation of editorial on Page 348)

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### BOOK REVIEWS

(Continued from Page 363)

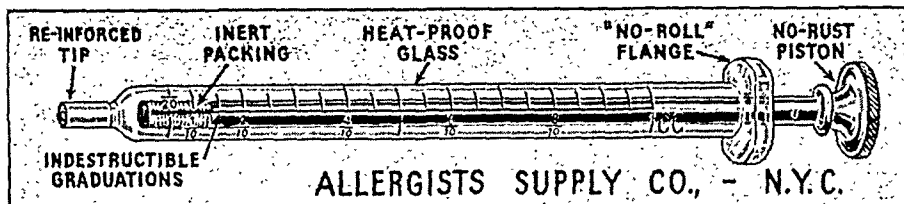
tigation of the secretory function of the digestive glands with the histophysiological and histochemical study.

There are thirty-one chapters including an extensive bibliography and index of authors as well as of subjects. The first third of the book is devoted to the structure and function of the digestive glands, a correlation of cytological with physiological data, digestive enzymes, histology, morphological and functional topography of gastric mucosa, and blood and nerve supplies; another third to the various chemical phases of gastric secretion including a thorough discussion of the role of histamine; while the last third contains a comprehensive discussion of the influence of the hormones on glandular activity and the role of the salivary glands.

The book is of good quality paper, is very easy to read, and the illustrations are varied and carefully selected throughout. The allergist interested in allergy of the digestive tract will gain valuable fundamental knowledge of the physiological processes necessary to understand the patho-physiological responses due to the mechanism of sensitivity. The book is indispensable to the internist and the general practitioner.

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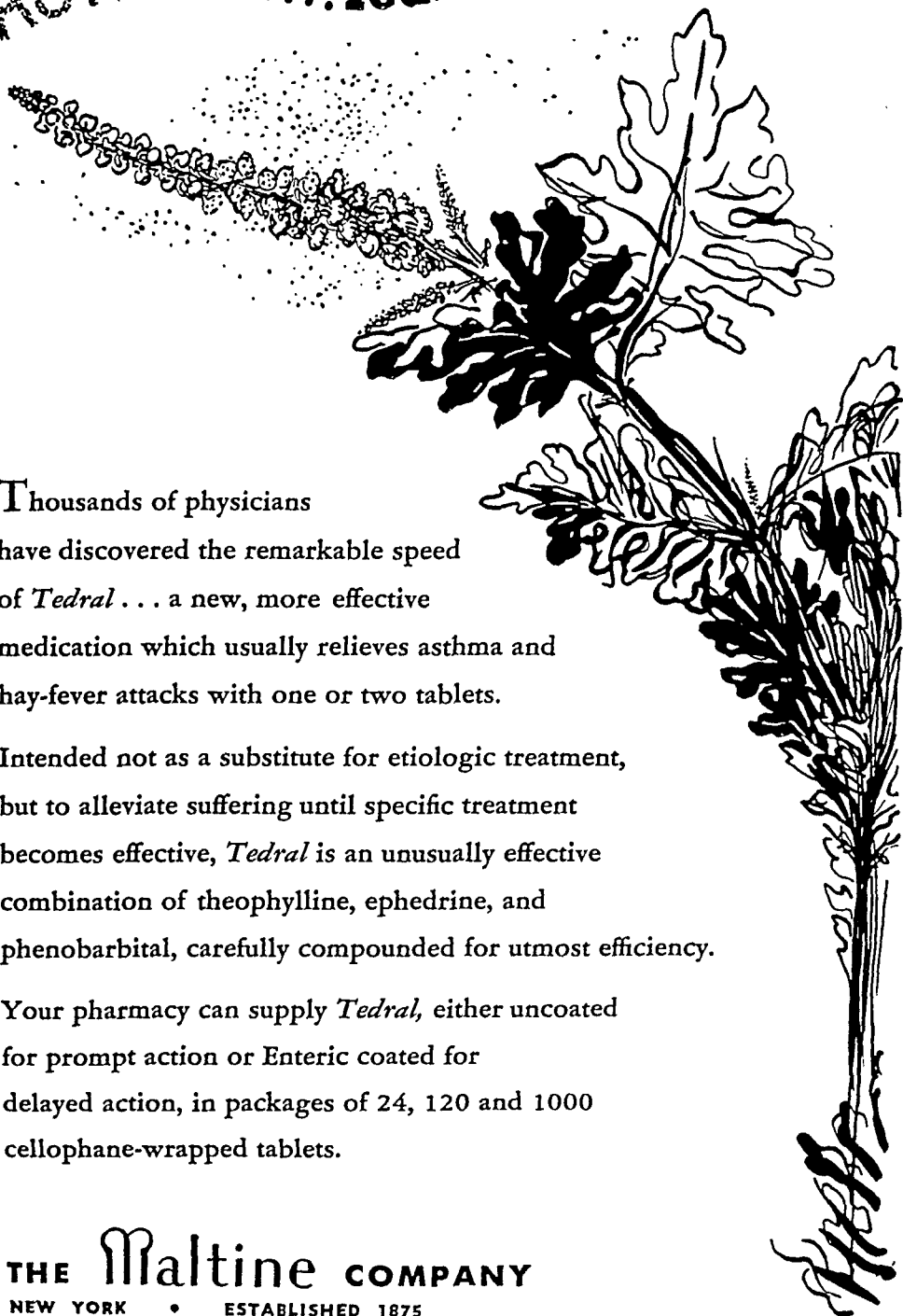
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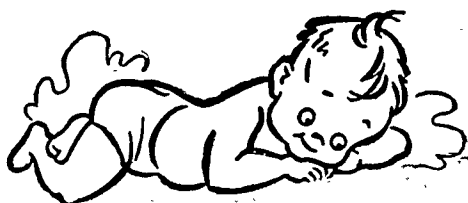
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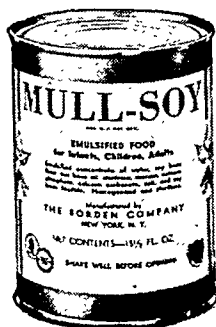
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Official Journal of the  
American College of Allergists

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634 North Grand Boulevard  
St. Louis 3, Missouri

Executive Office  
401 La Salle Medical Bldg.  
Minneapolis 2, Minnesota

**Annals of Allergy** is published bimonthly by the American College of Allergists. The contents of the journal consist of contributions in the field of diseases of allergy, book reviews, a current bibliography, editorials, case reports, new suggestions, questions and answers, news items and matters concerning the affairs of the American College of Allergists.

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All material for the current issue must be in the hands of the Editor by the fifteenth of the month preceding date of issue.

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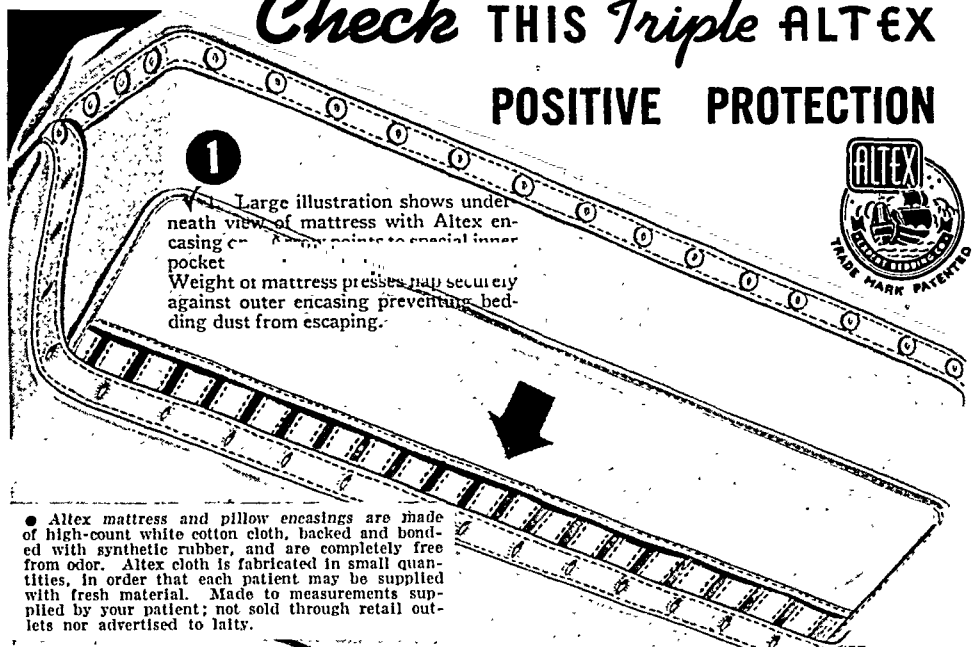
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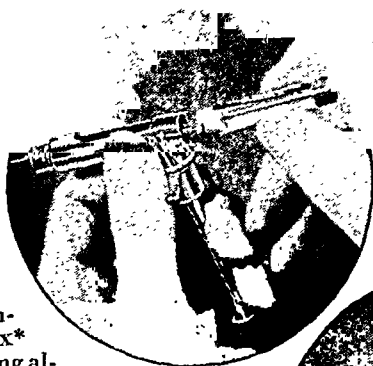
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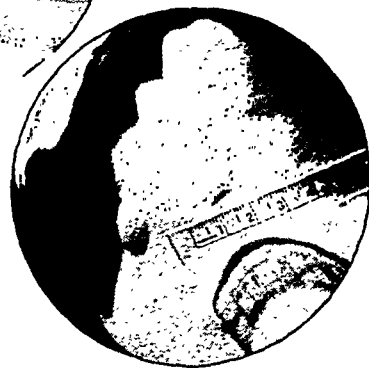
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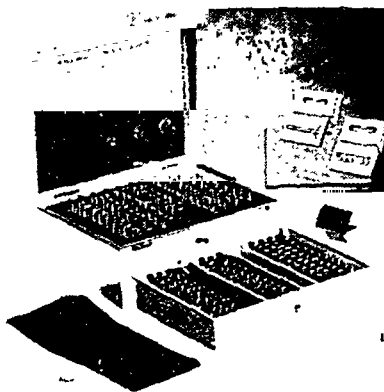


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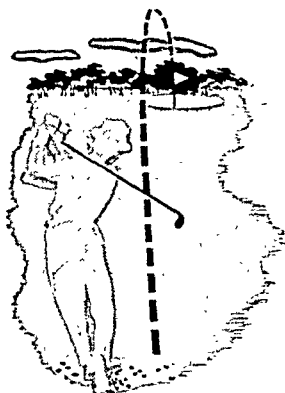
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## ARMY ALLERGY FOURTH SERVICE COMMAND 1943

COLONEL SANFORD W. FRENCH, MC, USA  
MAJOR LAWRENCE J. HALPIN, MC, AUS

Atlanta, Georgia

PREVIOUS reports<sup>1,2,3</sup> have emphasized the military importance of the allergic diseases. It is felt that a presentation of the clinical findings of the Allergy Section, Surgeon's Office, Headquarters Fourth Service Command, will lend additional significance to these groups of symptoms. The establishment of standardized diagnostic and therapeutic procedures has been productive of satisfactory results in the ambulatory duty patient, as well as effective of rapid and efficient administrative disposition of the disabled hospitalized allergic soldier.

During the past two years four short courses of instruction on the management of allergic diseases have been presented to a total of 180 medical officers. Changes in assignments and personnel transfers have determined the intervals at which these courses are conducted. As an aid to those officers whose training in allergy has been limited to their military experience, an active reprint and abstract file has been maintained to provide a source of reading material and reference in this specialty. Further recognition of the importance of allergy as a military medical factor is indicated by the interest shown in this section by units outside the limits of the Fourth Service Command. At the most recent allergy conference eleven medical officers from the Eighth, Seventh, Sixth and Third Service Commands were present. Standardized allergenic extracts are now supplied not only to our own clinics but to fifty-four station and general hospitals in the other eight service commands. The preparation, standardization and supply of these extracts by the Fourth Service Command Laboratory have not caused any interruption of, nor interference with, the routine laboratory procedures.

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<sup>1</sup>Presented at the first annual meeting of the American College of Allergists, June 10-11, 1944, Palmer House, Chicago, Illinois.



At the present time the Allergy Section, Office of the Surgeon, Fourth Service Command, supervises the investigation and therapeutic measures conducted in eighty-nine allergy clinics. Thirty of these are in service command station hospitals, eleven are in service command general hospitals and forty-eight are in Air Corps station hospitals. Of the officers in charge of these eighty-nine clinics, only twenty have had experience in allergy antedating their entrance on active duty. This is a point to remember when considering the number and types of patients, the symptoms and the indicated results to be discussed.

TABLE I. TOTAL PATIENTS—ALLERGY SECTION FOURTH SERVICE COMMAND  
November 1942 to November 1943

Clinics	Allergy	Derm. Ven.	Total
Service Command	20,220	5,305	25,525
Air Corps	4,984	1,537	6,521
Total for All Clinics	25,204	6,842	32,046

TABLE II. ALLERGY PATIENTS—ALLERGY SECTION FOURTH SERVICE  
COMMAND

Clinics	Army	Civilian	Total
30 Station Hospitals and 9 General Hospitals	18,869	1,351	20,220
28 Air Corps Hospitals	4,550	434	4,984
Total of 67 Clinics	23,419	1,785	25,204

Of the eighty-nine allergy clinics activated or in operation during 1943, sixty-seven of them had been instituted sufficiently long to present a report of the work done. Material for this report was gained from questionnaires submitted to each clinic and completed by the individual medical officer in charge of allergy work. The twenty-two clinics not included herein were of such recent activation that their material will be included in future compilations. A total of 32,046 patients were seen in all clinics reporting (Table I). Included in this figure are 6,842 cases of poison ivy dermatitis diagnosed in fifty clinics. The discussion and tabulation of the patients with dermatitis venenata has been given separate consideration. Most allergy clinics extended their services to civilian dependents, but the greatest number of patients were military personnel. Of the 25,204 patients with allergic symptoms of primary importance, 23,419 were of military status and 1,785 were civilian dependents (Table II).

The symptoms of seasonal hay fever were sufficiently severe to cause 5,373 patients to seek relief by specific pollen therapy (Table III). In a non-critical interpolation, it should be noted that severe seasonal hay fever is a cause for rejection from military service.<sup>5</sup> Ragweed pollen sensitivity has proven to be the outstanding single factor in producing the distressing

## ARMY ALLERGY—FRENCH AND HALPIN

symptoms of seasonal hay fever. A total of 1,796 patients limited their symptoms to the ragweed season only, while 747 were only grass pollen sensitive as indicated by the history and confirmed by skin testing. More patients, however, were both grass and ragweed pollen sensitive. In this classification there were 2,030 patients. It can be conservatively estimated that 85 per cent of these patients with uncomplicated seasonal hay fever were under specific therapy. This number of patients cannot be taken as an indication of the incidence of seasonal hay fever in the armed forces or even in the Fourth Service Command. Certainly there were many al-

TABLE III. SEASONAL HAY FEVER—ALLERGY SECTION FOURTH SERVICE COMMAND

Clinics	Grass	Ragweed	Combined	Total
Service Command (39)	608	1,193	1,553	4,154
Air Corps (28)	139	603	477	1,219
Total for 67 Clinics	747	1,796	2,030	5,373

TABLE IV. SEASONAL BRONCHIAL ASTHMA—ALLERGY SECTION FOURTH SERVICE COMMAND

Clinics	Grass	Ragweed	Combined	Total
Service Command (39)	129	265	425	819
Air Corps (28)	15	37	75	127
Total for 67 Clinics	144	302	500	946

lergic soldiers who did not avail themselves of therapeutic trial either because of the mildness of their complaints or for reasons which have not been brought to our attention.

For purposes of discussion, bronchial asthma can best be presented as those seasonal cases with and without associated hay fever and those with perennial symptoms with and without seasonal variation (Table IV). Pollen asthma without associated nasal or eye symptoms was the diagnosis in 946 cases. Ragweed pollen sensitivity is again outstanding among this group, there being 302 patients who limited their wheezing, cough and respiratory difficulty to this season. By comparing these with the 144 patients who admitted and demonstrated only a grass pollen sensitivity and with those 500 cases whose complaints existed during both the grass and ragweed seasons, the importance of this particular fall pollen is further emphasized. The association of seasonal hay fever symptoms with those of seasonal bronchial asthma is recorded for 1,384 patients (Table V). Undoubtedly, many soldiers in this group were experiencing their initial asthmatic complications. The explanation for this rests perhaps in the degree of exposure to pollen as a result of their training maneuvers, their bivouacs and their inability to adequately control that degree of "over-ex-

# ARMY ALLERGY—FRENCH AND HALPIN

posure." There were 690 patients in this group who had symptoms of pollen sensitivity during both the grass and ragweed seasons. Some of these may have had symptoms limited to one or the other season prior to their military service, and the above environmental influences must be considered. Of these 1,384 patients, 512 of them were pollen sensitive only to ragweed and 182 limited their complaints to the grass season.

Perennial bronchial asthma has been responsible for the appearance of 7,261 patients in the sixty-seven allergy clinics (Table VI). Only 1,903 of these gave a history and findings suggestive of seasonal variation due

TABLE V: SEASONAL HAY FEVER AND ASTHMA—ALLERGY SECTION  
FOURTH SERVICE COMMAND

Clinics	Grass	Ragweed	Combined	Total
Service Command (39)	167	449	515	1,131
Air Corps (28)	15	63	175	253
Total for 67 Clinics	182	512	690	1,384

TABLE VI. PERENNIAL BRONCHIAL ASTHMA—ALLERGY SECTION  
FOURTH SERVICE COMMAND

Clinics	With Seasonal Variation	Without Seasonal Variation	Total
Service Command (39)	1,586	4,254	5,840
Air Corps (28)	317	1,104	1,421
Total for 67 Clinics	1,903	5,358	7,261

to pollen, while 5,358 of them denied such exacerbations. Most of these perennial asthmatics were dust sensitive by history and by skin test. Other etiologic factors were chiefly of the inhalent type. In isolated instances, food allergy was considered of primary importance, but always in association with secondary inhalent sensitivities. There is a definite difference between the asthmatic seen in a station hospital and the soldier with asthma admitted to a general hospital. In most reports the listed causative factors for asthma in the station hospital have been pollen, dust and feathers. Reports from the eleven general hospitals in the Fourth Service Command place the additional element of infection high on the list for etiological consideration. This would imply that the more stubborn and therapy-resistant asthmatic problems are seen in the general hospitals. Certainly more so-called "intrinsic" asthma is seen at these installations. The soldier with bronchial asthma is a problem not only within the continental limits of the United States, but in the various battle areas as well. The allergy section at one general hospital<sup>4</sup> has shown that 86 per cent of the bronchial asthmatics on the wards have been evacuated from overseas. In many of these patients the original onset of asthma started in that part of the world from which they had been returned. Complete relief was experienced by some of them on the return sea voyage, with continued

## ARMY ALLERGY—FRENCH AND HALPIN

freedom from symptoms being noted since their hospitalization in this country. All too frequently, however, there is obtained the long history of pre-induction asthma that has been aggravated by the rigors and exigencies of foxholes and mud. These patients are not mold sensitive by skin test, nor have any other factors been definitely ascertained in the search for the basic or contributing etiology.

Bronchial asthma, therefore, is seen to be the most important allergic disease to the Army. This is apparent from the frequency with which this diagnosis has been made and the disabling properties possessed by these

TABLE VII. SUMMARY OF BRONCHIAL ASTHMA—ALLERGY SECTION  
FOURTH SERVICE COMMAND

Clinics	Seasonal Asthma	With S.H.F.	Perennial	Total
Service Command (39)	819	1,131	5,840	7,790
Air Corps (28)	127	253	1,421	1,801
Total for 67 Clinics	946	1,384	7,261	9,591

TABLE VIII. PERENNIAL ALLERGIC RHINITIS—ALLERGY SECTION  
FOURTH SERVICE COMMAND

Clinics	With Seasonal Variation	Without Seasonal Variation	Total
Service Command (39)	856	2,001	2,857
Air Corps (28)	249	725	874
Total for 67 Clinics	1,105	2,726	3,831

symptoms. A summary of the bronchial asthma seen in sixty-seven clinics reveals 9,591 patients to have been diagnosed and treated (Table VII). One might expect the perennial asthmatic to be disqualified for military service more readily than the inductee with seasonal symptoms. In both service command and Air Corps clinics, however, the presence of perennial symptoms has been outstanding. Of the total number of asthmatic patients seen in the clinics, 76 per cent (7,261) of these definitely had symptoms throughout the year. The diagnosis of perennial asthma was made upon the history in the presence of symptoms and not upon the history alone. These figures add emphasis to the difficulty encountered by an induction board of medical officers in making an honest, though hurried evaluation of a patient's history. It must be admitted that the perennial asthmatic does not make a capable, physically reliable fighting soldier. If he is retained in service his duties must be assigned within the variable limits of his physical endeavors. His problem, as it concerns us, is one not limited to immediate diagnosis, therapy and administrative disposition; it is a problem that will be with us for many years when claims for benefits are made and collected.

Persistent, year-around complaints of nasal congestion and discharge were factors in bringing 3,831 patients to the allergy clinics (Table VIII).

## ARMY ALLERGY—FRENCH AND HALPIN

Perennial allergic rhinitis was not particularly disabling, but the discomfort resulting from the persistency of symptoms was marked. The diagnosis in each case was based on a history which, in most instances, dated the original onset of complaints many years prior to their clinic visit. The usual patient first presented himself to the nose and throat clinic from where he was referred for allergy investigation. Nasal smears for eosinophilia were done on most of these patients. This has been an important aid in establishing the diagnosis upon an allergic basis. A seasonal increase in the severity of their symptoms was noted by 1,105 of these

TABLE IX. MISCELLANEOUS ALLERGIC DISEASES—ALLERGY SECTION  
FOURTH SERVICE COMMAND

Cases	Service Command (39)	Air Corps (28)	Total
Urticaria	1,343	301	1,644
Migraine	661	158	819
GI Allergy	232	23	255
Food Allergy	1,446	119	1,565
	Total for 67 Clinics		4,283

patients. The lack of any seasonal aggravation was determined in 2,726 instances. Essentially the same causative factors as were listed for perennial bronchial asthma are offered in this classification. Dust, feathers and pollen sensitivities were most frequently recorded. Any association between nasal and bronchial perennial symptoms in the same patient has not been clarified in our tabulation, as each patient has been classified on a basis of his primary complaints and diagnosis.

Chronic urticaria has been a source of disturbance and discomfort to the individual soldier as well as to the attending medical officers (Table IX). Ultimate disposition of these cases involves the determination of the causative factors, the degree of resulting disability and the type of duty to which the patient has been assigned. Acute urticaria is no more a problem to the medical officer than it is to the civilian practitioner. The chronicity of symptoms, however, places the additional burden of responsibility for proper administration upon the Army allergist. A thorough search for the etiologic factors has been advocated and a therapeutic trial of elimination and evaluation has been established in all clinics. In all, 1,644 patients with a diagnosis of acute or chronic urticaria were seen in the sixty-seven clinics included in this presentation. Allergy investigation and study have definitely been responsible factors in retaining the majority of these patients on a duty status. It can surely be assumed that the broad program of immunization for military personnel has been an effective originator of many initial attacks of urticaria. In some instances, the lesions from such sources have continued over a rather prolonged period of time.

The diagnosis of migraine was recorded in 819 cases. This classification has been included under miscellaneous allergic diseases in this discus-

## ARMY ALLERGY—FRENCH AND HALPIN

sion. Gastro-intestinal allergy, of which there were 255 cases, has been differentiated from food allergy. In this latter group there were 1,565 patients. In our tabulation there is undoubtedly an occasional duplication of diagnosis in the same patient. The complaints of these soldiers with food allergy have not been listed separately, as it has been our experience that the patient with a marked allergic reaction to a food or group of foods is usually capable of dietary elimination insofar as it is compatible with his military food rations. This statement is based upon the knowledge that the greatest majority of these symptoms due to food sensitivity wheth-

TABLE X. HOSPITAL CASES—ALLERGY SECTION FOURTH SERVICE COMMAND

Cases	Service Command (39)	Air Corps (28)	Total
Seasonal Hay Fever	473	129	602
Bronchial Asthma	4,444	1,003	5,447
Other Allergic Cause	1,746	344	2,090
	Total for 67 Clinics		8,139
Hospital Days	148,285	24,170	172,455

er they be migrainous, gastro-intestinal or the like, are of importance secondary to the more severe, more frequent and more manifest allergic respiratory complaints seen in the Army clinics.

The efficiency of a capable, well-trained fighting force is primarily based upon the physical fitness, stamina and proficiency of the individual soldier. That efficiency is directly concerned with an uninterrupted training program. The retarding influence of the allergic diseases upon that same military efficiency is emphasized when consideration is extended to the hospitalization resulting from these symptoms. It must be remembered that the necessity of hospitalizing the military allergic patient is greater than for the civilian patient. No comparison, therefore, can be drawn between the two, nor can this necessity be interpreted as a failure of therapeutic measures. The Army will hospitalize the patient for whom the civilian physician, under similar circumstances, would recommend a daily rest or less arduous labors. Over a period of twelve months, 8,139 allergic patients were admitted to the hospital wards (Table X). This represents 32.3 per cent of the total military allergic patients. Of this number, only 602 were diagnosed uncomplicated seasonal hay fever of sufficient severity to warrant absence from duty. Bronchial asthma was responsible for by far the greatest majority of this 32 per cent. This diagnosis was recorded for 5,447 patients. Unfortunately, no definite indication has been given as to the classification of these asthmatics, but from previous tabulations perennial asthma may safely be considered as the outstanding offender. Hospitalized patients for other allergic reasons numbered only 2,090. This adds further importance to the role played by bronchial asthma as an impediment to the successful conclusion of this war.

The vast quantity of time lost from training because of the incompatibil-

## ARMY ALLERGY—FRENCH AND HALPIN

ity between duty and severe allergic complaints can be realized with the recognition that 172,455 days were spent by these patients in the hospitals. An average of 21.2 days for each patient is revealed. In some branches this represents one-third of their initial period of training. The implication should not be taken, however, that all of this hospital time was necessitated by the severity of the complaints nor by the failure of therapeutic

TABLE XI. DISPOSITION OF CASES. CERTIFICATE OF DISABILITY DISCHARGE—  
ALLERGY SECTION FOURTH SERVICE COMMAND

Clinics	S.H.F.	Asthma	Other Cause	Total
Service Command (39)	89	2,724	358	3,171
Air Corps (28)	17	507	47	571
Total for 67 Clinics	106	3,231	405	3,742

### DISPOSITION BOARD

	Service Command	Air Corps	Total
Returned to duty	8,266	2,307	10,573
Certificate Disease Disability	3,053	574	3,627

response. It must be stated that in some instances the wheels of administrative procedure turn slowly for discharge from the Army. In spite of this frank admission, these total hospital days represent additional work and detail for the medical officer, additional discomfort to the individual soldier and additional expense to the Government.

In the disposition of an allergic soldier, a board of medical officers considers the severity or persistency of the symptoms, the response to therapy and the professional opinion of the attending medical officer. It has been advisable in the Fourth Service Command to add one other consideration, the importance of which merits special mention and emphasis. A patient whose outstanding military or scholastic qualifications are of particular use to the Army is reassigned to a type of duty compatible with his symptoms and his potential disability. This reassignment is made with the assurance that the attending allergist is competent, experienced and well qualified to extend to that patient the best of care, advice and treatment. Such disposition is productive of dual benefits—the soldier is the recipient of expert allergy management and the Army avails itself of his essential experience and knowledge.

There are instances, of course, where the only correct procedure is the discharge of an allergic soldier. No definite standards can be established upon which such disposition can be determined. The duration, frequency, persistency, severity and etiology of the complaints are variable in the allergic diseases and in the allergic patients. Uncomplicated seasonal hay fever hardly warrants a Certificate of Disability Discharge. Seasonal sneezing, nasal congestion, nasal discharge, and lacrimation were respon-

sible for only 106 disability discharges (Table XI). These cases may have had some complications or the response to therapy may have been discouraging. Bronchial asthma was the diagnosis in 3,231 discharges. In all cases the severity of the symptoms was such that continuation on active duty was an impossibility. It is reasonable to assume that many of these cases should never have been admitted to service with the armed forces. In spite of such an assumption, however, all cases were closely analyzed and investigated in order to assure the correct disposition. Only 405 patients were discharged because of the disabling characteristics of other allergic complaints. Thus, with a total of 3,742 Certificates of Disability Discharge having been ordered because of allergic symptoms, 86.3 per cent were due to bronchial asthma. The significance of asthma is again emphasized by these self-evident tabulations. After appearing before a disposition board, 10,573 allergic patients were retained in service and returned to a type of duty consistent with their complaints.

It should not be expected that therapeutic results in the military management of allergic diseases would equal those obtained in civilian practice. There are many factors in explanation of this viewpoint. Environmental control, comparatively easy and adequate in civilian life, is practically an impossibility in military medicine. A camp or bivouac site may be in the midst of an abundant ragweed growth. A barracks housing thirty to forty men can hardly be prepared in a dust-free or feather-free manner. The suitable application of dietary regimens in the average Army mess is an insurmountable obstacle to proper food elimination therapy. In spite of these factors, satisfactory therapeutic results can be obtained. An indication of such results is offered in reviewing the number of cases that have been discharged from the service and those which have been retained on a duty status. In the sixty-seven clinics included in this report, only 106 patients were separated from the service because of seasonal hay fever. During the same period, 5,373 hay fever patients were receiving pollen therapy. This serves as an indication that specific pollen therapy was surely beneficial to many allergic soldiers. The total figures for bronchial asthma are even more impressive. This diagnosis was recorded for 9,591 patients. Of these, 3,231 were eventually discharged from the Army because of the persistent severity of their symptoms and their failure to respond to the prescribed therapy. Allergy care and management, therefore, can be considered as being directly responsible for retaining 6,360 soldiers on duty. Similar indications of benefits can be derived from a perusal of the number of miscellaneous allergic diseases causing discharges, as compared to the total number of these cases seen in the clinics.

Specific pollen therapy has been instituted upon a pre-seasonal or a co-seasonal basis. In some few instances, perennial therapy has been suggested, but this, as a rule, has been inadvisable from the military standpoint. Very good results have been obtained with conservative, low-dosage pollen extract administration.



There has been established a good degree of liaison between the allergy clinics and the induction centers. The decision as to the acceptance or rejection of an allergic applicant is made after the patient has been seen in consultation by the attending allergist. This procedure has resulted in a more correct interpretation of the patient's complaints, a more accurate evaluation of the potential disability and a more acceptable basis upon which to place the rejection or the admission of the allergic inductee.

The Allergy Section of the Surgeon's Office, Fourth Service Command, has been in activation since March 1942. Since that time, 180 medical officers have been trained in the care of the allergic patient and eighty-nine clinics have been established. These clinics are operating as a closely welded unit for the purpose of extending to the allergic soldier the best of diagnostic acumen, care, treatment and disposition.

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#### DISCUSSION

LT. COL. LOUIS E. LIEDER, MC, AUS, Washington, D. C.: The importance of accumulating significant data on allergic diseases in the military service, so well done by Colonel French and Major Halpin, cannot be overestimated. There has been very little, if any, established precedent to follow in the disposition of allergic patients from military hospitals. This need, to a great extent, is supplied by the careful analysis and interpretation of findings in the Fourth Service Command. Individualization of the patient cannot, of course, be neglected in a consideration of prognosis and disposition of the allergic, but the study conducted by the Allergy Section, Surgeon's Office, Headquarters, Fourth Service Command, gives the medical officers in station and general Army hospitals a working basis for the proper recommendations in disposition of allergic patients.

The large number of both hospitalized and outpatient, duty status allergic patients reported points to the need and importance of proper assignments, especially in general hospitals, of the limited number of physicians trained in the specialty of allergy. This will facilitate the care and proper disposition of allergic persons, reduce the length of hospitalization, and prevent frequent, prolonged and unnecessary rehospitalizations.

Because of the not infrequent transfer of military personnel from one service command to another, a program for expansion of the laboratory facilities for preparation and standardization of allergic extracts, the proper training of medical officers at least in the fundamentals of allergic diagnosis and treatment, and the establishment of allergy clinics for both inpatient and outpatient care, is indicated and necessary. This would prevent unnecessary hospitalization and lessen the non-effective rate considerably, thereby aiding the war effort.

The allergy clinic can act as an invaluable adjunct to the induction station and to the physical examining section in evaluating fitness for overseas duty, for officers' candidate school, and for proper classification of the individual soldier.

## ARMY ALLERGY—FRENCH AND HALPIN

From my point of view in a general hospital, I would like to emphasize the importance of limiting the asthmatic patients, who are not discharged from military service, to the continental limits of the United States. As will be shown in a brief review of 186 consecutively hospitalized asthmatic patients in 1943 at a general

### AGE AT ONSET OF ASTHMA

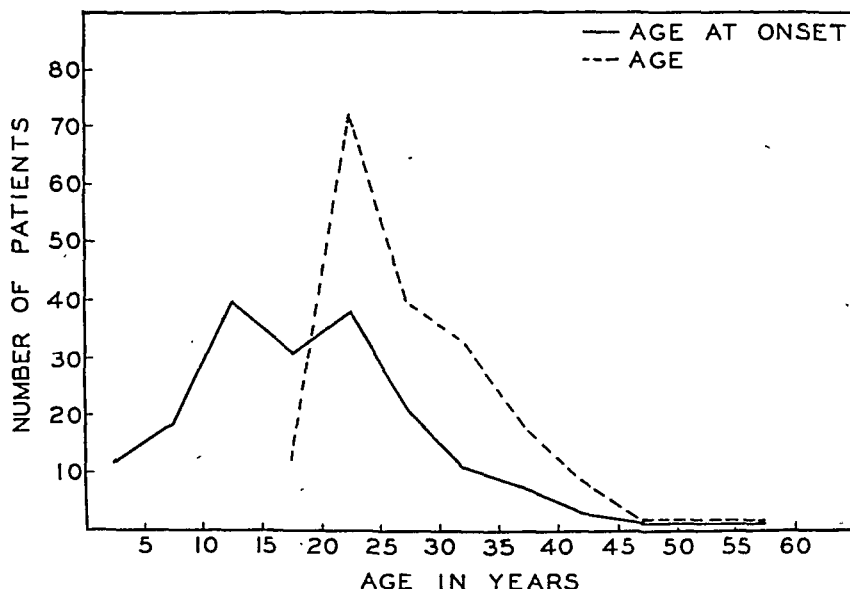


CHART I

hospital, exacerbation, invalidization, and hospitalization in overseas theatres is not uncommon, and the patients must be returned to the one of the interior. Many of our patients who had mild or infrequent asthma in the states were invalidated and unable to carry on with duty within a very short period of time in many of the overseas theatres. The importance of weeding out these soldiers prior to embarkation for overseas duty is apparent.

TABLE I. CASES OF ASTHMA ANALYZED

	No.	%
White .....	175	94
Colored .....	11	6
Extrinsic Asthma .....	141	76
Intrinsic Asthma .....	45	24
Fam.ly History of Allergy.....	116	62
Total .....	186	100

As Leopold has pointed out, it is not infrequent to find asthmatic individuals returned from overseas theaters who had never had allergic symptoms in the United States prior to this duty. Preventive allergy screening cannot, of course, be carried out for this group.

*Analysis of 186 Hospitalized Asthmatic Patients.*—In reviewing 186 consecutive admissions for asthma in Walter Reed General Hospital in 1943, the following information was obtained:

One hundred seventy-five patients (94 per cent) were white and eleven (6 per cent) were colored (Table I). The asthma was extrinsic in type in 141 (76 per cent)

## ARMY ALLERGY—FRENCH AND HALPIN

and intrinsic or bacterial in forty-five (24 per cent). Almost all of the extrinsic asthmatic patients were found to have multiple inhalant sensitivities by intradermal skin tests. A positive family history of allergy was recorded in 116 (62 per cent) of the patients.

The age range of the patients was from eighteen to sixty years with 95 per cent of the group falling in the young adult age group of twenty to thirty-five years, as would be expected in the military service (Chart 1). The age of onset of asthma as shown in the table was most frequent in childhood and decreased rapidly after the age of twenty-five years.

TABLE II. TIME OF ONSET OF ASTHMA

	No.	%
Prior to Military Service.....	140	75
During Military Service .....	46	25
Total .....	186	100

Although Mobilization Regulations 1-9 state that asthma of any degree is disqualifying for induction into the army, 140 (75 per cent) of this series of asthmatic patients had the onset of their asthma prior to military service (Table II). Apparently rejection of inductees because of asthma is not being carried out in all cases as prescribed by regulation.

TABLE III. SITE OF ONSET OF ASTHMA

	No.	%
Overseas Onset .....	29	15
Africa .....	2	1.0
Bermuda .....	1	0.5
England .....	2	1.0
Hawaii .....	1	0.5
India .....	1	0.5
Panama .....	7	4.0
Puerto Rico .....	15	8.0
United States .....	157	84.5
Total .....	186	100.0

Approximately 85 per cent of this group developed asthma in the United States; while twenty-nine patients (15 per cent) had an overseas onset. The exact place of onset is shown in Table III.

TABLE IV. EXACERBATION OF PRE-EXISTING ASTHMA  
ON OVERSEAS DUTY

Total Patients .....	186
Africa .....	15
Bermuda .....	1
Egypt .....	3
England .....	24
Iceland .....	1
India .....	3
Iran .....	1
Ireland .....	2
Italy .....	2
Palestine .....	1
Panama .....	10
Puerto Rico .....	5
Sicily .....	3
Total .....	71
Of total patients 38% had exacerbation of pre-existing asthma.	

Asthma apparently is frequently exacerbated by overseas service. Seventy-one patients (38 per cent) of the 186 asthmatic persons studied fall in this category (Table IV). It was especially noted that intrinsic or bacterial asthmatics developed symptoms within a short time after arrival in England. Many were given short trials of duty and required repeated hospitalizations before they were returned to the zone of the interior.

Of the total number of 186 patients, twenty-nine (15 per cent) had their first symptoms of allergy in overseas theatres and seventy-one (38 per cent) had ex-

## ARMY ALLERGY—FRENCH AND HALPIN

acerbation in the overseas theatres (Table V). One hundred patients (53 per cent) of the total hospital admissions for asthma began during or were exacerbated by overseas duty.

TABLE V.

	No.	%
Onset of Asthma Overseas .....	29	15
Exacerbation of Asthma Overseas.....	71	38
Total .....	100	53
Total Asthmas Studied.....	186	100

This group of 100 asthmatic patients were analyzed as to the course of their symptoms after return to the zone of the interior, that is, the continental limits of the United States. In 42 per cent the asthma was entirely relieved and they were asymptomatic during their entire period of hospital observation (Table VI). Most of this group were followed for at least two months during which time they were granted convalescent furloughs without having any recurrence of asthma. Thirty-five per cent had mild and infrequent attacks after return to the United States, 21 per cent had moderate asthma, while 2 per cent continued to have severe and frequent paroxysms.

TABLE VI. COURSE AFTER RETURN TO ZONE OF INTERIOR

No Asthma .....	42
Mild Asthma .....	35
Moderate Asthma .....	21
Severe Asthma .....	2
Total .....	100

Disposition.—The disposition of hospital patients of any type must depend to a great degree upon the requirements of the military service as well as the medical condition of the men. When limited service as such was abolished in August, 1943, (War Department, Circular Letter No. 161, 14 July, 1943) mild and asthmatic patients as well as other patients with mild or moderate physical handicaps were discharged on a certificate of disability. Then when the manpower problem became more acute and limited duty personnel were needed, mild and moderate asthmatics were kept in the service in restricted capacities conforming to their physical abilities (War Department, Circular Letter No. 293, 11 November, 1943).

Since many asthmatic soldiers and those with other manifestations of allergy are being retained in the military service, an adequate program for their care is essential.

TABLE VII. DISPOSITION OF ASTHMATIC PATIENTS

	No.	%
Returned to Limited Duty.....	91	49.2
Discharged from Service .....	94	50.8
Total .....	185	100

Disposition was carefully determined for 185 asthmatic patients excluding a retired sergeant who continued in a retired status. Of these ninety-one (49.2 per cent) were returned to a limited duty status and ninety-four (50.8 per cent) were discharged on a certificate of disability (Table VII).

It is interesting to break down the figures on disposition of the asthmatic patients into (1) those with onset overseas, (2) those with exacerbation overseas, and (3) those without overseas duty (Table VIII). In the first group consisting of twenty-nine patients, twenty-six were returned to limited duty and three were

discharged, 90 per cent and 10 per cent, respectively. Approximately half of the seventy-one patients with exacerbation overseas were returned to duty. Of the patients without overseas duty, eighty-five in number, only thirty-one (36 per cent) were returned to duty and fifty-four (64 per cent) were discharged from the service.

NUMBER OF ARMY HOSPITALIZATIONS  
FOR ASTHMA

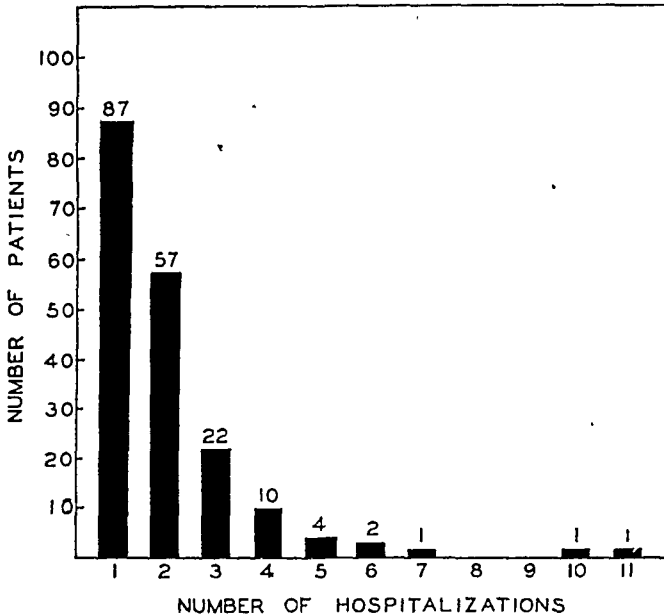


CHART II

Although the number of patients with onset of asthma in the overseas theatres was relatively small, it seems significant that only 10 per cent continued to have symptoms after return to the United States, requiring their separation from the service. It would appear that the prognosis for rapid recovery in this type of case is excellent.

TABLE VIII. DISPOSITION OF ASTHMATIC PATIENTS

<i>Onset Overseas</i>	No.	%
Limited Duty .....	26	90
CDD .....	3	10
Total .....	29	100
<i>Exacerbation Overseas</i>		
Limited Duty .....	34	48
CDD .....	37	52
Total .....	71	100
<i>Without Overseas Duty</i>		
Limited Duty .....	31	36
CDD .....	54	64
Total .....	85	100

In view of the relative frequency of exacerbation of symptoms on overseas duty, it was deemed inadvisable to permit any asthmatic who was returned to duty, to be assigned to overseas duty. They were therefore limited to duty in the continental limits of the United States.

## ARMY ALLERGY—FRENCH AND HALPIN

Because of the frequent history of repeated previous army hospitalizations, an analysis of this point was made. It was found that fifty-seven patients had two hospital admissions for asthma and twenty-two patients had three (Chart 2). One patient had ten and another eleven separate periods of hospitalization. This is another good reason for restricting even mild asthmatics to the continental limits of

### LENGTH OF SERVICE PRIOR TO DISCHARGE

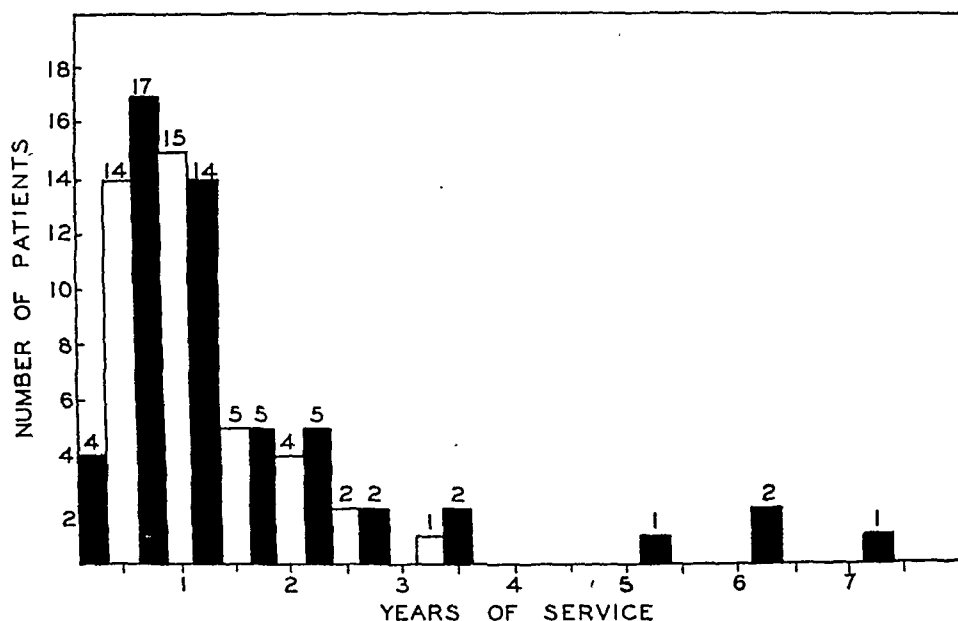


CHART III

the United States. Otherwise, beds needed for combat casualties would be occupied by asthmatic patients.

Moderate and severe asthmatic persons in this series of patients were unable to keep up with the military pace and as noted above were frequently discharged on certificate of disability. How long was it before these patients required and were granted their discharge? Of the ninety-four asthmatic patients discharged, sixty-four were separated from the service within a year and a half.

On the whole, from the foregoing data it would appear that asthmatic persons as a rule do not do well in military service. They are frequently invalided, require frequent hospitalizations, and after a relatively short period of duty, about half must be separated from military service.

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DIAPHRAGMATIC DYSPNEA. Day, Lt. G. H.: J. Roy, Army M. Corps, 81: 290, (Dec.) 1943.

The commonest disorder of the respiratory system in the British Army would appear to be a dyspnea resulting from faulty diaphragmatic function. Symptoms appear late in military training. Physical signs are usually suggestive of "emphysema." Diagnosis is usually made by fluoroscopic examination which shows the excursion of the diaphragm to be slight, absent or paradoxical. Breathing exercises are recommended as therapy.—L.J.H.

## ALLERGIC SKIN DISEASES IN THE NAVY

COMDR. MARION B. SULZBERGER, MC, USNR

New York, New York

BECAUSE of the requirements of the Service, the men and women of the Navy form a selected group. This selection tends to reduce the incidence of certain diseases; for example, those of infancy, of old age, many congenital anomalies, et cetera. On the other hand, there are in the Navy, and inherent in Naval duties and occupations, many factors which tend to increase the relative incidence of certain forms of illness. Allergic cutaneous diseases are undoubtedly among the manifestations which might be expected to appear in the Navy in an incidence somewhat higher than that found in the general population. The diets of naval personnel—balanced and excellent as they, of course, are—do not enable an individual to observe the rigorous avoidance of his possible food allergens. Immunizing procedures of proven efficacy, drugs, vaccines and sera given prophylactically must be administered to *every* individual, in order to protect the health of the community, of shipmates and to maintain the fighting efficiency of the Service. And most important of all, the clothing and equipment used and the materials contacted at work must perforce be standardized and of quite constant ingredients. No man on duty can select what he can or cannot wear or use. He must use and wear that which is supplied to him and to his fellows. When a man has the misfortune to be allergic to an item of general issue, it is as a rule utterly impossible for him to even attempt to avoid the offending agent.

The clear realization of this fact and of its full implications highlights two important points in relation to military medicine—and in particular in relation to allergy in the Armed Forces. (1) Every reasonable effort must be made to keep out of the Armed Forces those persons who are known to be allergic or who are likely to become strongly allergic; in other words, to keep the "index of sensitivity" of the personnel as low as possible. (2) Every effort must be made to reduce as far as possible the general distribution and use of any materiel which has a distinct tendency to sensitize and to produce allergic reactions. In other words, items intended for general use and general issue should be rigorously examined for their "sensitizing index" before they are approved and adopted.

Thus clothing, shoes, socks, paints, dyes, cleansers, insect repellents, anti-sunburn creams and lotions, venereal disease prophylactics, innumerable other "issue" materials which contact the skin, as well as numerous items purchasable in the ship's service stores, might well be tested not only for their merits in regard to value, quality, and durability, but also

Presented at the first annual meeting of the American College of Allergists, June 10-11, 1944, Palmer House, Chicago, Illinois. The opinions or assertions contained in this article are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

in regard to their allergenic nature and capacity for producing contact dermatitis. An efficient method for accomplishing such tests consists in the use of the patch test in the manner which Dr. Adolph Rostenberg, Jr., and I<sup>2</sup> first described for determining the "sensitizing index" of different agents.

An illustration of the really tremendous role which such elimination or reduction of potential sensitizing agents might play can be seen in the recent report on "Textile Dermatitis" by Davies and Barker.<sup>1</sup> These authors report that during six months there were 670 admissions to the skin wards of a large military hospital, and of these 110 (16.4 per cent) were "wholly or partly due to intolerance by the skin of contact to woollen textiles" (clothing or blankets). Even if these figures appear rather high, no experienced military dermatologist will deny the tremendous role played by clothing and wools in the production of incapacitating skin diseases in the Armed Forces.

Due to the nature of my duties, my own contacts with clinical cases of allergic dermatoses in the Navy have been rather meager during the last two years—and I am certain, therefore, that Dr. Leider, who has consented to discuss my report, will be able to give you a more detailed, personal, and lively exposition—not only of clothing dermatitis, but also of the many forms of allergic dermatoses and the many types of allergens encountered in the Navy.

I shall, therefore, confine myself to the presentation and brief discussion of some figures which I trust you will find interesting and instructive in relation to the nature and importance of allergic skin diseases in the Navy. These figures were assembled for the purpose of this presentation by Lt. (jg) T. D. Woolsey (H)V(S) USNR and Mrs. H. M. Voss of the Section on Vital Statistics, at the request of Captain T. J. Carter (MC) USN of the Division of Preventive Medicine, of the Bureau of Medicine and Surgery, of the Navy Department. I am indebted to them for placing these data at my disposal.

The statistical analysis includes the three years, 1940, 1941 and 1942, and the figures for 1943 insofar as they were available up to May 31, 1944. The incidence and sick days given for skin diseases are likely to be quite accurate, whereas in calculating the figures for allergic skin diseases some rather arbitrary decisions had to be made. Thus, for the purposes of these statistics all cases of "eczema," "dermatitis," "urticaria," "angio-neurotic edema," et cetera, were considered to be "allergic," whereas in point of fact a significant proportion of such cases may not have been on an allergic basis. Moreover, all fungous dermatoses ( a very large group indeed) have been included under "allergic." However, there was no way to determine what proportion of these diseases were due primarily to allergy and what to other mechanisms, and I was left no choice but to include the totals. It is, therefore, fair to state that all figures given for allergic skin diseases are surely too high and that they must be discounted



# ALLERGIC SKIN DISEASES IN THE NAVY—SULZBERGER

somewhat, perhaps by as much as 30 to 50 per cent, if they are to represent only allergic skin conditions in the usual and more restricted sense.

Table I gives the new admissions for the groups of diseases under consideration and the total new admissions. "New Admissions" indicates that the patient was never previously admitted to the Naval Sick List because

TABLE I. ALLERGIC DERMATOSES IN THE NAVY

Totals	1940	1941	1942	1943
New Admissions skin diseases	7,993	13,827	33,539	75,363
allergic skin diseases	1,815	3,384	8,875	22,101
all diseases	90,162	136,296	343,996	not available
Sick Days skin diseases	115,153	188,468	398,512	765,386
allergic skin diseases	37,310	64,250	130,195	278,237
all diseases	1,583,335	2,634,326	5,957,371	not available

TABLE II. ALLERGIC DERMATOSES IN THE NAVY

Ratios	1940	1941	1942	1943
$\frac{\text{New Adm.—skin diseases}}{\text{New Adm.—all diseases}}$	8.9%	10.1%	9.7%	not available
$\frac{\text{New Adm.—allergic skin diseases}}{\text{New Adm.—all skin diseases}}$	22.7%	24.5%	26.5%	29.3%
$\frac{\text{New Adm.—allergic skin diseases}}{\text{New Adm.—all diseases}}$	2.0%	2.5%	2.6%	not available

of that particular complaint. Thus, if a man is admitted twice or three times for asthma, he still appears correctly as only one case—his admissions subsequent to the first being classified as "Readmissions" and not included in the table.

The table indicates clearly the growth of the Navy and the corresponding increase in skin diseases and allergic skin diseases.

Table II shows that about one case in ten on the Naval Sick List is admitted because of some skin disease. Of course, many cases of skin diseases are not admitted, but can be treated while the man is on full duties. My own experience indicates that if such minor cases were included, it is conservative to estimate that this would about double the present figures for incidence.

Of the skin diseases admitted to the Sick List about one in four were classified as allergic or possibly allergic. On this basis allergic skin diseases account for about 25 per cent of the 10 per cent incidence of skin diseases—in other words, for about 2.5 per cent or one in forty of all admissions.

# ALLERGIC SKIN DISEASES IN THE NAVY—SULZBERGER

Table III shows that the number of days lost because of skin diseases represents about 7 per cent of the total days lost because of illness. Since the figures for admissions show that about 10 per cent of all admissions are due to skin disease, the 7 per cent figure here suggests that patients with dermatoses may get off the sick list in somewhat less time than does

TABLE III. ALLERGIC DERMATOSES IN THE NAVY

Ratios	1940	1941	1942	1943
<u>Sick days—skin diseases</u> <u>Sick days—all diseases</u>	7.3%	7.2%	6.7%	not available
<u>Sick days—allergic skin diseases</u> <u>Sick days—all skin diseases</u>	32.4%	34.1%	32.7%	36.4%
<u>Sick days—allergic skin diseases</u> <u>Sick days—all diseases</u>	2.4%	2.4%	2.2%	not available

TABLE IV. ALLERGIC DERMATOSES IN THE NAVY

Ratios	1940	1941	1942	1943
<u>EPTE—all skin diseases</u> <u>(EPTE + new adm.)—all skin diseases</u>	2.6%	3.4%	5.0%	4.4%
<u>EPTE allergic skin diseases</u> <u>EPTE + new adm.)—allergic skin diseases</u>	1.8%	2.9%	5.1%	3.9%
<u>EPTE—all diseases</u> <u>(EPTE + new adm.) for all diseases</u>	8.8%	11.7%	15.7%	not available

the average case. But allergic skin diseases, although having an incidence of about one-quarter of the admissions for all skin diseases, account for slightly over one-third of the sick days for all dermatoses. This suggests that cases of allergic skin diseases stay on the Sick List somewhat longer than the average for other dermatologic cases.

Table IV shows what proportion of the allergic skin diseases admitted to the Sick List were found to have existed prior to enlistment (EPTE). It will be seen that about 3.8 per cent of all skin diseases admitted were proven to have been present before enlistment, and 3.4 per cent of all allergic skin diseases were shown to have existed prior to enlistment. In contrast to this, about 12 per cent of all the cases on the Naval Sick List were there because of illnesses which had existed prior to enlistment. These figures appear to me to be rather noteworthy, since they suggest that among Naval personnel skin diseases and allergic skin diseases appear in a relatively high proportion of individuals who have never suffered from similar complaints before entering the service. In other words, when compared with the general run of illnesses, skin diseases and allergic skin disease are about three times as likely to have their onset at *some time after* entering the Naval service.

# ALLERGIC SKIN DISEASES IN THE NAVY—SULZBERGER

Table V shows the number of cases and the days lost because of asthma, because of hay fever, because of allergic dermatoses and because of skin diseases in general. Here it will be seen that when contrasted with dermatoses and allergic dermatoses, hay fever and even asthma are rather insignificant causes of illness and disability in the Navy.

TABLE V. ALLERGIC AND OTHER CONDITIONS IN THE NAVY

Admissions	1940	1941	1942	1943
Hay Fever	15	53	81	not available
Asthma	108	307	1,176	not available
Allergic Dermatoses	1,815	3,384	8,875	22,101
All Dermatoses	7,993	13,827	33,539	75,363
Sick Days				
Hay Fever	399	1,787	1,534	not available
Asthma	9,788	17,087	52,592	not available
Allergic Dermatoses	37,310	64,250	130,195	278,237
All Dermatoses	115,153	188,468	398,512	765,386

\* \* \*

I believe that the figures presented make it clear that skin diseases, including allergic skin diseases, constitute one of the major problems of military medicine. Much progress has been made through the recognition of this fact by the Medical Corps of the Armed Forces, both during and immediately preceding the present war. The Surgeon General of the Navy and the Research Division of the Bureau of Medicine and Surgery are keenly interested in the subject of dermatoses and allergic dermatoses. This interest has not been only an abstract one, for the Bureau has continued to encourage and approve every reasonable project which promised to advance our knowledge and improve our treatment in this group of conditions.

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## DISCUSSION

LT. COMDR. MORRIS LEIDER, MC, USNR, Pensacola, Fla.: Commander Sulzberger is one of the easiest persons to argue with, but one of the hardest to refute. Moreover, he invites and encourages disagreement, dispute for the constructive purpose of eliciting other opinion and thus leads to a pooling of thought. Since his paper is largely statistical, I find I could forego the pleasure of the cerebral fisticuffs we usually engage in, thus probably saving myself some figurative black eyes. However, with more foolhardiness than courage, I shall immediately invite an intellectual brawl by some peculiar interpretations of the data presented by Comdr. Sulzberger.

First, I submit the following propositions:

## ALLERGIC SKIN DISEASES IN THE NAVY—SULZBERGER

1. Disease effects based on allergic mechanism are increasing in absolute numbers. This is easy to understand apart from the greater discovery rate resulting from better understanding of allergic reactions in conditions which were previously without known cause. The tremendous increase in gross number and complex variety of industrial agents and consumer goods, the unprecedented relocation of large populations in unusual places and precipitation into novel circumstances, and the unusually rapid tempo of current work and life are factors in an absolute increase of diseases of allergy.

2. Disability from allergic effects in the military group is large, as has just been demonstrated.

3. In general, prophylaxis against disease is more effective, easier, and cheaper in the long run than cure. When it comes to individual cure of established disease versus prevention by a prophylactic technique, preferably a public health measure, the preventive mode wins hands down every time. In all of medicine, I can think of no disease or group of diseases that has been cured out of existence by treatment of every case. All of this is especially true of the diseases of allergy. Therapeutic specifics are unknown and not to be expected of discovery. Successful curative regimes by desensitization procedures are few and irritatingly uncertain. The great hope in the abatement of diseases of the allergic mechanism lies in (a) avoidance of the establishment of the altered, specific reaction-response and (b) avoidance of the offending agent when the altered specific reaction-response has been established. And between (a) and (b), the former is the more desirable solution of the problem; to wit, in general prevent the establishment of an allergic state.

From these three propositions I draw clear conclusions for military medicine, i.e., military preventive medicine only, because opportunities for employing traditional therapeutic modalities for diseases of allergy, even where rarely effective, are hopelessly involved and difficult of exhibition in the Navy. These conclusions are:

1. Common and special military gear, namely uniforms, shoes, hats and helmet linings, sartorial accessories generally, rubber, plastic and metal gadgets ought to be tested as materials and in processing for allergic potential before the quartermaster orders them by the millions. Specialists such as compose this group are proper technicians and authorities.

2. The greatest single class of allergenic substances that causes harm to the soldier population is cosmetics, common hygienic agents like soaps, powders, and dentifrices, and self-applied medicaments. It would profit the military much to develop soaps, dentifrices, powders, shaving preparations, pomades, hair oils and the rest of the peripheral hygienic and beautifying substances—develop such things of minimal allergic potential and distribute them G.I., i.e., gratis or at trivial cost. The promotion of needless, super-civilized beautifying agents by commercial fraud is a barbarism scarcely less than that of the rigors of war. Official indifference to this phenomenon, the plethoric stocking in post exchanges and ship's stores of dozens of brands of metriciously packaged, cheaply scented, irrationally medicated, and overpriced personal articles is to be deplored as wasteful and harmful. The appearance of women in war service is, to my viewing, a desirable and progressive thing, but from their sea chests full of potentially harmful accessories to beauty, it is sometimes hard to remember that there is a hell of a war going on somewhere.

3. An ideal opportunity exists in military medicine for study of allergic phenomena which, it may be seen by the least prophetic, are going to plague the world more than ever as time passes.

# ALLERGIC SKIN DISEASES IN THE NAVY—SULZBERGER

## SERVICE ALLERGIES

Offending Agents, Precipitating Factors or Sources of Allergy	Remarks
Common and special military gear Shoes, hats, socks, uniforms, helmets/linings/ rubber clothes, plastic and metal accessories, et cetera	Allergic effects are commonly seen but not readily appreciated by allergically unconscious medical officers. Significance lies in obvious sense of testing materials and processes before the quartermaster orders a billion items.
Cosmetics and self-applied external medications. Particularly medicated soaps, sulfa ointments, patent medicines, et cetera	Allergic effects commonly seen. Promotion of needless beautifying agents by commercial ads and official indifference is to be deplored. G.I. issue of tested soaps, dentifrices, powders, shaving preparations, pomades, hair oils, etc., would be profitable.
Agents used in VD prophylaxis Condoms, chemicals	Allergic reactions surprisingly rare or inconsequential (fortunately)
Internal medicaments in legitimate treatment	Allergic phenomena commonly seen but not too rapidly recognized. About the same problem as in civil practice.
Service Chow	Much the same problem as in civil life except less possibility of carrying out reasonable variation.
Immunizing procedures	Allergic phenomena commonly seen from large volume of inoculations done but serious effects rare.
Regional agents and native habits, e.g., insects, fish, animals, plants, native foods	Allergic effects are common and a difficult problem.
Psychic factors: Hostility to rigid discipline, poor morale, strain of military responsibility, tendency to malingering	These factors activate allergic diatheses, precipitate allergic crises and generally mess things up.
EPTE† allergies	Pre-existing allergies tend to be aggravated by the physical and psychological milieu of military service. Adequate medical attention is not provided. On the other hand, some few cases get better, not worse, while in military service.

†Existed prior to enlistment.

In brief then, this war period and its industrial hurly-burly should force an examination of the direction of allergy in the postwar state. Since the number of problems to be solved postwar will be legion, it adds but little to the total burden to consider where and how we needlessly or avoidably make ourselves wretched with allergic discomforts. This is not to say that we need be timid in the development and use of new agents that may enhance human fruitfulness, but it would be well to test and certify materials, processes and uses for their "sensitizing index" before irresponsible commercial and other promotion leads to a rash of rashes.

## A NOTE ON CYSTS AND ABSCESES INDUCED IN THE RAT BY THE INJECTION OF OILS. Emery, F. E., and Mathews, C. S.: J. Lab. & Clin. Med., 28:1795, (Dec.) 1943.

Oil (1 c.c.) was injected intramuscularly in hind leg of rat and the site examined two days to one year later for oil, hemorrhage, durability of cyst wall and abscesses. All oils tested (mazola, olive, cottonseed, sweet almond, sesame and peanut) formed cysts. Abscesses were present in nearly one-half the rats injected with sweet almond oil, and in a few with cottonseed oil. Aseptic technique had no bearing on the incidence of abscess. With thickness of cyst capsule as indicator, sesame oil is more irritating than mazola, olive and peanut oils. All four failed to induce gross inflammation. Sweet almond and cottonseed were therefore considered most irritating.

L. J. H.

# ALLERGIC OCCUPATIONAL DERMATITIS IN OUR WAR INDUSTRIES

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**B**EFORE we can proceed with this subject it is necessary to define what is meant by "war industries" and what we shall consider to be allergic dermatoses.

Although almost everything we do is directly or indirectly connected with the war, we shall only consider for the purpose of this paper as war industries, the manufacture of arms, ammunition, airplanes, ships, synthetic rubber, and wearing apparel for the use of our armed forces. The author's conception of allergic dermatoses requires a more lengthy explanation.

## DEFINITION OF ALLERGIC DERMATOSES

The chemical causes of occupational dermatoses may be divided into primary irritants and sensitizers.<sup>1</sup>

A PRIMARY CUTANEOUS IRRITANT is an agent which will cause dermatitis by direct action on the normal skin at the site of contact if it is permitted to act in sufficient intensity or quantity for a sufficient length of time.

A CUTANEOUS SENSITIZER is an agent which does not necessarily cause demonstrable cutaneous changes on first contact but may effect such specific changes in the skin that, after five to seven days or more, further contact on the same or other parts of the body will cause dermatitis.

A primary irritant has a definite chemical or physical action on that portion of the skin with which it comes in contact. It forms a chemical combination with the skin or abstracts essential ingredients from it, resulting in total destruction, burn, or in inflammation depending on the concentration of the chemical and the period of exposure.

A primary irritant may also be a sensitizer. Exposure to it may so condition the skin that further contact with even such dilute solutions or for such a short time as would not before have caused any trouble, may now result in dermatitis.

Undoubtedly deficiencies in the defense mechanism of the skin renders it more vulnerable to the action of primary irritants. Every one is sensitive to the action of primary irritants, but those having physiologic, anatomical, or traumatically inflicted defects of the skin are hypersensitive. Such a hypersensitivity is not specific and the resulting dermatitis is due to the chemical or physical action of the chemical on that particular portion of the skin. Any other primary irritant may have the same effect. The hypersensitivity is localized to the vulnerable area of the skin. For in-

<sup>1</sup>From Dermatoses Section, Industrial Hygiene Division, Bureau of State Services. Presented at the first annual meeting of the American College of Allergists, June 10-11, 1944, Palmer House, Chicago, Illinois.

stance, ammonium nitrate in solution has but little effect on the normal skin, but will attack sites of abrasion. Such a dermatitis should not be called allergic. Dermatitis should only be called allergic if it occurs as a result of an induced generalized sensitivity after a period following exposure to a substance which is not a primary irritant in the concentration to which exposure occurred.

For instance, a wool dyer with apparently normal skin develops dermatitis after exposure for seven days to a dye containing 0.5 per cent of potassium dichromate, and patch tests on distant sites of normal skin with this concentration give positive reactions. Potassium dichromate in strong concentration is a primary skin irritant, but 0.5 per cent will not affect the normal skin.<sup>2</sup> Therefore, such a dermatitis can be called allergic.

Then again, a worker with tetryl or TNT will work for seven days or more before developing dermatitis, and patch tests on distant sites of normal skin give positive reactions. This is also allergic because neither TNT nor tetryl will affect the normal skin.

Such an induced sensitivity or allergy is specific and present all over the skin. It is not confined to any particular vulnerable area.<sup>3</sup> However, it is also true even in allergic dermatitis that open abrasions or sites having thin layers of epithelium may be more sensitive than normal areas of skin.

There is no sensitivity, before exposure, to substances that are not primary irritants, but five days or longer after exposure a certain percentage of those exposed become sensitized. The percentage sensitized is directly proportional to the degree of exposure. For instance, about two per cent of workers handling small tetryl pellets become sensitized and develop dermatitis, whereas, 50 per cent of those working in the tetryl-drying house, where they are covered with tetryl dust, develop dermatitis.

The term hypersensitivity should be used when speaking of primary irritants because every one is sensitive to them. Allergy, or specific sensitivity, should only be applied to induced or acquired sensitivity which becomes manifest after a period of incubation following initial contact. It is present over the entire skin. Allergy is often followed by a hyposensitization or tolerance. This is usually the case when contact with the causative agent is continued for a sufficient period, i.e., long enough for the dermatitis to disappear, two to four weeks.<sup>4</sup> Tolerance may also follow recovery from the dermatitis even though the recovery occurred after contact with the causative agent was discontinued. The tolerance developed is only to the degree of exposure, i.e., the concentration of the chemical and the amount and duration of exposure to it. Higher concentrations, exposure to greater amounts, or exposure for longer periods of time, may result in a recurrence of dermatitis, followed by again developing a tolerance to the greater exposure.<sup>5</sup> It requires continuous exposure to maintain the tolerance. The tolerance developed is lost if exposure ceases for a time. The time that the tolerance persists after exposure ceases, varies with the individual. In some cases tolerance lasts only for one or two

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weeks, in others for several months. If there is re-exposure after this period, dermatitis will again occur and tolerance may again be developed.

In cases where tolerance has been present for many years and dermatitis suddenly occurs while there is continued exposure to only the same degree, tolerance does not again develop, perhaps because the immunity mechanism has broken down. Such a worker should be removed from exposure.

Undoubtedly breaks in the defense mechanism of the skin also make it easier for allergens to enter and cause sensitivity. Such breaks may consist of thin layers of epithelial cells, abrasions, deficient or abnormal glandular secretions. After sensitivity is established the eruption may appear at sites other than the site where the allergen first entered, as for instance:

In cases where the allergen causing sensitivity is also taken into the system through the digestive or respiratory organs and deposited in the skin, dermatitis may occur on sites where there has been no contact. In such cases dermatitis may become generalized.

Tolerance is not developed to the primary irritating action of a substance, except insofar as the anatomical and physiological deficiencies of the skin which make one hypersensitive may be remedied, as for instance:

Tolerance may be developed to primary irritation caused by mechanical forces, such as calluses occurring as a result of friction and preventing further irritation, and to physical forces such as actinic rays by tanning and thickening of the epithelial layer thus preventing further damage by the actinic rays.

Now that we have defined our concept of war industries and allergy, we will proceed to describe the allergic dermatoses in our war industries.<sup>5</sup>

### EXPLOSIVES

The explosives causing most cases of allergic dermatitis are tetryl, TNT, fulminate of mercury, ammonium picrate, and an explosive known as R.D.X.

Tetryl (Tetranitro-methylanile) is a light yellowish solid. It is a sensitive explosive used in making boosters, fuses, and demolition bombs. It causes a higher percentage of allergic dermatitis than any of the other explosives. From 2 to 50 per cent of exposed workers are sensitized depending on the degree of exposure. More than 90 per cent of those developing allergic dermatitis from it also develop a tolerance, especially if they continue at work. This is proven by the fact that most of the cases occur among new workers and that the incidence of tetryl dermatitis in our ordnance plants has fallen steadily. That recurrences occur when the exposure is increased, was dramatically illustrated in one plant where workers who had developed a tolerance to handling tetryl pellets and TNT were put to work at pouring tetratol bombs, which entails a much greater exposure. After ten days there was an outbreak of dermatitis which in the next four months affected about 300 workers or about 50 per cent of



those engaged in the operation. They were treated and kept on the job and again developed a tolerance to this greater exposure so that after the fourth month there was only one active case.

Tetryl causes yellow staining of the hands and hair. It causes nosebleed because of congestion of the nasal mucosa. The dermatitis affects chiefly the face, although the hands and arms may also be involved. In severe cases the eyelids are swollen shut. The dermatitis usually lasts for two or three weeks. Treatment of acute cases consists in the application of wet dressings of boric acid or Burow's solution (1-20) until most of the edema subsides, after which boric acid ointment may be applied. Severe cases should be taken off the job, especially while the wet dressings are being applied.

Mild cases should be given a protective application for use on the face and kept at work.\* They should be given boric acid ointment to use on the face after work. Most of them will get well while working and will develop a tolerance which usually lasts for two weeks or more after stopping work.

The prevention of dermatitis from tetryl consists of (1) efficient exhausts under dusty operations; (2) clean closely woven coveralls furnished daily; (3) wearing of washable light leather gloves fitting snugly over the wrists to prevent entrance of tetryl; (4) compulsory supervised showers after work. In some ordnance plants new workers are first placed in jobs where there is a minimum contact with tetryl and after two or three weeks they are given jobs involving more contact and so on until they have developed a tolerance to the jobs where there is most contact.

TNT is a yellowish-brown solid and is a nonsensitive explosive used as a bursting charge in shells, bombs, and mines.

TNT causes sensitization dermatitis, but not in as high a percentage of those exposed as does tetryl. It affects chiefly the hands where it causes edema, papules, and deep-seated vesicles, especially on the palms. The wrists and forearms are also affected and sometimes the face. A few cases of generalized dermatitis have occurred in which even the soles were affected. When the dermatitis subsides the skin on the palms desquamates in large flakes.

TNT in the air in the form of dusts or fumes causes a bitter taste. It is absorbed into the system and causes aplastic anemia. In such cases the worker is usually cyanotic with blue lips.

The treatment of TNT dermatitis and its prevention is similar to that described under tetryl except that respirators should be worn on all jobs where there is an exposure to TNT dust or fumes.

\*A greaseless application developed by the U. S. Public Health Service was found to give protection to about 25 per cent of sensitized workers. It leaves a dry adherent deposit on the skin, rendering it difficult for tetryl to get through.

It consists essentially of:

Shellac .....	12
Carbitol .....	2
Sod. perborate.....	10
Isopropyl alcohol.....	56
Titan. oxide.....	20

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Fulminate of mercury is a sensitive explosive even more so than tetryl. It is used in detonators and primers. It will cause small ulcers if it enters abrasions, but its chief action is that of a sensitizer. Only small amounts of it are handled and in some places it is loaded while wet, yet dermatitis is of frequent occurrence. It affects the face, where soiled hands touch it and also the arms, especially the cubital spaces.

The treatment and prevention are the same as for TNT and tetryl.

Ammonium picrate and picric acid are used as bursting charges. They cause yellow discoloration of the skin and hair and sensitization dermatitis which usually affects the face.

Dermatitis occasionally occurs among workers handling smokeless powder. It is usually due to sensitization to dinitrotoluol or diphenylamine which smokeless powder contains in small amounts. Dermatitis from lead azide and pentaerythritol tetranitrate is rare.

There has been a tendency among workers making and loading cartridges to call all skin irritations "brass poisoning." Brass is an alloy of copper and zinc and while it is possible that a rare individual may become allergic to these metals, the large majority of so-called "brass poisonings" are caused by some other substance. Dichromates used to brighten brass, alkaline coolants used in making the cartridges, and zinc chloride used in soldering, are often the causative agents in so-called "brass poisoning."

### CUTTING OILS<sup>6,8</sup>

In the manufacture of large and small arms, the cutting oils and solvents are the principal causes of dermatitis, but these are primary irritants. However, cutting oils especially the insoluble ones, may contain phenolic amines as inhibitors, and as antiseptics, and these sometimes sensitize a worker and cause eczematoid dermatitis, which in no way resembles the cutting oil acnes and the dermatitis caused by the primary irritant action of cutting oils and solvents.

There are, however, certain sensitizing chemicals used as rust preventives to protect bright polished steel pieces, and these often cause allergic dermatitis.

The prevention of allergic dermatitis caused by inhibitors used in cutting oils and rust preventives is to have the workers wear synthetic rubber gloves with impervious sleeves fastened over the gloves at the wrist, and impervious aprons.

Recently we have found that cobalt used in the alloy of which cutting tool edges are made, can cause allergic dermatitis.

We have not observed any tolerance developing in workers affected with allergic dermatitis from cutting oils and rustproofing compounds. This may be because the small amounts of the allergens contained in them are not sufficient to cause desensitization.

In the foundries connected with the manufacture of cannon, tanks, and automotive equipment, allergic dermatitis occurs from resins and oils, especially fish oils used in making molds and cores.

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In the manufacture of airplanes allergic dermatitis<sup>10,11</sup> occurs from resins and fish oils used as protective coatings for sheets of duralumin and Dow metal while in shipment, and also from the potassium bichromate content of chrome yellow, used as a primer coat on airplane wings and fuselage. The term "dural poisoning" is used by airplane workers to designate cases of dermatitis occurring among them. While it is possible that a rare person may become allergic to the metals in the aluminum alloys, many patch tests on cases of "dural poisoning" performed by the author with duralumin and Dow metal have yielded no positive reaction. "Dural poisoning" is usually caused by some other irritant. In plywood manufacture for airplanes, dermatitis occurs from the synthetic resin glues.

**Synthetic rubber:** There are many types of synthetic rubber, but at present Buna S is the one principally used by our armed forces. It is made by the copolymerization of butadiene and styrene. Butadiene is made from butylene, an ingredient of crude petroleum. Styrene is made from propane which is also found in crude petroleum.

In the manufacture of styrene there is but little allergic dermatitis. The tertiary butyl catechol used as an inhibitor to keep styrene from polymerizing while being shipped and stored, is a primary irritant and sensitizer. The dermatitis caused by it is usually due to accidental splashes and is caused by primary irritation.

Styrene itself is a primary irritant and sensitizer, and in styrene plants accidental splashes of it may cause primary irritation.

In the polymerization plants allergic dermatitis occurs from sensitization to tertiary butyl catechol, because the exposure in these plants is to great dilution, no more than 10-200 parts per million. Such dilutions are not primary irritants. The same thing is true of styrene, the workers only coming in contact with it in such dilutions in the rubber, as does not affect the normal skin, but sensitizes a small percentage of those exposed.

Other sensitizers in the manufacture of Buna S are the anti-oxidant phenylbetanaphthylamine and some of the coal tar derivatives such as Bardol and Sulfol. All of these chemicals are also photosensitizers.

In the processing plants allergic dermatitis may occur from accelerators and antioxidants as well as from small amounts of unpolymerized styrene remaining in the rubber and given off as a vapor when the rubber is heated in the mix mills.

### SHIP BUILDING

In the building of ships allergic dermatitis may occur from molds, cores, oils, and paints, as described above.

### FABRICS

Fabrics used by our armed forces often require special dyeing and finishing. In plants making woollens, where the dyeing formerly was done with 0.5 per cent of potassium dichromate as a mordant, the government

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specifications called for 3 per cent and the old workers who had developed a tolerance to 0.5 per cent broke out with dermatitis soon after 3 per cent dichromate was used. Most of them again developed a tolerance to the 3 per cent.

Some of the fabrics must be finished with mildewproof and waterproof chemicals. All the mildewproof chemicals are primary irritants in strong concentration, and many are sensitizers in even such low concentrations as .2 per cent. Allergic dermatitis has occurred among workers sewing and handling fabrics processed with certain antimildews.

Japan wax made from a member of the *Rhus* family, and used as a waterproofing material on fabrics, caused allergic dermatitis among workers sewing the fabric.

Allergic dermatitis may also occur from some flameproof chemicals used in fabrics.

The diagnoses of all occupational allergic dermatitis is made by considering the occupational history, knowing the sensitizing properties of the chemicals occupationally encountered and the performing of patch tests.

The history must show that the dermatitis occurred after the lapse of a period of incubation, following contact with the substance. This period of incubation is at least five days or longer. Inquiry should show that not all the workers similarly exposed were affected. This shows that the substance is not a primary irritant. The sensitizing properties of the chemicals which the workers contact should be ascertained. Patch tests performed with the actual substance suspected of causing the dermatitis should be performed in proper dilutions on those affected, as well as on controls. The substance causing allergic dermatitis should show a positive reaction on those affected while the eruption is active, and a negative reaction on the controls. If the controls also react, the substance is a primary irritant.

### SUMMARY

Allergic occupational dermatitis occurs more frequently in the manufacture of munitions than in other war industries.

Tolerance develops in most workers who develop allergic dermatitis, if they are treated while working.

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### DISCUSSION

SAMUEL M. PECK, Sr. Surgeon (R) USPHS, Bethesda, Md: The attention of dermatologists and allergists has been drawn to the role of allergy as a cause of industrial dermatitis to such an extent that too often they have lost sight of the fact that less than 20 per cent of all occupational skin diseases are due to sensitizers.

It is obvious from Dr. Schwartz's paper that a state of hypersensitivity in the broad sense may exist as far as skin reactions to chemical irritants are concerned which is not on an allergic basis. This more susceptible state of the skin to injury by primary irritants is due to differences in natural, anatomical and physiological barriers to the action of these irritants in different individuals.

Such natural protective barriers are the thickness of the keratin layer, the amount and constituents of the lipoids covering the skin surface and the pH of the skin surface. The presence of breaks in these barriers which are caused by direct injury and the action of chemical and physical agents play a role in the production of dermatitis of industrial origin whether it is due to a primary irritant or a sensitizer.

In order to induce an allergic contact dermatitis an intimate contact between the allergen and the living cells of the epidermis is necessary. Any factor or factors which tend to facilitate such contact play an important role in the production of the allergic state. Thus the properties of the allergen as far as its capabilities of passing through the natural barriers of the skin is concerned, and the action of environmental factors which destroy these natural barriers must be understood in order to control and prevent outbreaks of industrial dermatitis.

Electrolytes are poorly absorbed, if at all, through the intact epidermis and only small amounts are absorbed through the skin appendages. For this reason such factors as tiny wounds and scratches, friction, maceration of the skin, exposure to strong alkalis and fat solvents, and many other such moments which help absorption of the electrolytes by removing the natural barriers account for the sensitization to them.

These contributory factors to the development of the hypersensitivity state play an especially important role in the development of industrial dermatoses. A study of the dermatitis due to zinc chromate (i.e., potassium dichromate), cobalt, and other such chemicals clearly indicate that a factor such as friction places an important role in the development of sensitivity to them. Substances which are water and lipid-soluble are absorbed more readily than electrolytes through the intact epidermis and the skin appendages. Prolonged contact with such chemicals in an industrial process often lead to the development of cases of allergic dermatitis. Such an instance was brought out in a study of dermatitis due to carrots.<sup>†</sup> The causative agent was both ether and water soluble.

Fat solvents play an important role in the production of dermatitis due to primary irritants and sensitizers. By removing the surface fats, they eliminate one of the

<sup>†</sup>Peck, Samuel M., Spolyar, Louis W., and Mason, Howard S.: Dermatitis from carrots. *Arch. Dermat. & Syph.*, 49:266-269, (Apr.) 1944. Reprints.

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natural protective barriers. In addition, they attack the phospho-lipid membrane around the living cells and thus facilitate penetration of chemicals into the cells.

Some insight on the localization of dermatoses in general has been gleaned from a study of the localization of industrial dermatoses. Here again, the localization depends on contact between the chemical and the living cells. The dermatitis first occurs at places where there is the greatest concentration of the chemical in contact with the living cells.

It is for this reason that industrial dermatoses are most often seen on uncovered areas of the body and in areas especially exposed to friction. If the exposure to the chemical is the same all over the body the localization of dermatitis will depend on the thickness of the epidermis, especially the keratin layer, the amount and the constituents of the lipoids on the skin surface, etc. It is in this way that friction by bringing about more intimate contact of the chemical in greater concentration for a given length of time determines many of the localizations of industrial dermatoses, whether due to primary irritants or sensitizers. However, in cases where we have extreme sensitivity or the dissemination of the allergen takes place through the blood stream, and some allergen reaches the skin, the anatomical and physiological barriers play a more minor role and we get a widespread distribution of the eruption.

Our experience with the results of patch tests and a consideration of the preceding discussion makes one skeptical of the existence of the so-called localized sensitivity. It is usual to base conclusions on the existence of the local hypersensitivity from the observation that a dermatitis repeatedly appears on the same area of the skin and the fact that patch tests performed with a given concentration of the allergen are only positive in and around the area where the dermatitis occurs. Unless the localized area of dermatitis is due to a hematogenously disseminated allergen, the diagnosis of local hypersensitivity must be reviewed with consideration for the variation of the physico-chemical barriers in different areas of the body. Given the same degree of sensitivity over the entire body, patch test reaction can be elicited in the same period of time only over areas of skin which resemble each other in the thickness of the epidermis, in the lipoids on the skin surface, et cetera. After such considerations and the illustrations in Dr. Schwartz's paper, it can be readily seen that differences in hypersensitivity of the skin on a non-allergic basis may well explain the localization of a dermatitis due to a sensitizer.

Several illustrations can exemplify the reasons for the localization of a dermatitis even though there is a generalized sensitivity. TNT dermatitis is usually seen on the palms. Most cases of allergic contact dermatitis are seen on the dorsum of the hands while the palms remain unaffected. This is due to the fact that in most instances, while chemicals are probably contacted by the palmar surface of the hands more often than other areas of the body, yet because of the continuous perspiration which occurs on the palms and soles and on no other parts of the body, the chemicals are constantly being removed; in addition, the palms are covered with a relatively thick keratin layer.

One of the characteristics of TNT workers is the yellow stain of the skin of the palms. This indicates that the chemical is not being washed off by the perspiration and eventually penetrates to the living cells and sensitizes them. It is not infrequent also to see the localization of dermatitis due to fumes and dusts on the eyelids because the keratin layer is very thin there and the constant movement of the eyelids promotes friction. Another example of the reason for the localization of the dermatitis is the observation that workers sewing cloth impregnated with anti-mildew usually develop their dermatitis on those portions of the forearms where they are exposed to the greatest friction and thus indicate contact with the impregnated fabric. The sensitivity to the anti-mildews is present all over the body.

*(Continued on Page 439)*

# ALLERGY IN RELATION TO THE GENITO-URINARY TRACT

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THE purpose of this paper is to discuss allergy as related to the genito-urinary tract and to present case histories which either substantiate or suggest the existence of certain allergies. The parts of the genito-urinary tract will, therefore, be considered as shock organs in an allergic response. Allergic manifestations involving the genito-urinary tract are not common, but the infrequency of occurrence does not deny their existence nor minimize their importance. A diagnosis of genito-urinary allergy is made only by exclusion.

## REVIEW OF THE LITERATURE

The extensive smooth muscle and mucous membrane surface of the genito-urinary system make it an ideal shock organ for an allergic reaction. It has been demonstrated experimentally that smooth muscle spasm occurs in the bladder and uterus when specific allergens are injected into previously sensitized animals. Manwaring and Marion<sup>14</sup> presented proof that bladder allergy does exist and substantiated their evidence by the production of an allergic reaction in rabbits.

Duke<sup>6</sup>, who placed great emphasis on possible allergic reactions in the genito-urinary system, reported the occurrence of bladder symptoms as related to food allergy in the absence of a pathologic condition or in the presence of a minor pathologic condition in the urinary tract. The most common symptoms were bladder tenesmus, painful urination, varying degrees of pain with soreness over the bladder, and polyps from chronic allergic edema. "There are some patients who suffer frequent painful urination with constant pain over the bladder, out of all proportion to lesions found after careful examination by internist, urologist, and roentgenologist. They are treated under various diagnoses, but the symptoms continue as severely as before. These symptoms have been proven definitely in certain cases to be due to hypersensitiveness to certain foods."

Osler<sup>16</sup> in 1895 reported cases of glomerulonephritis attributable to Henoch's purpura of long standing. Alexander and Eyerman<sup>2</sup> considered this condition to be due to an underlying allergy. Thomas and Forsythe reported a patient having hematuria with a diagnosis of allergic purpura due to tar fumes.<sup>21</sup> Since 1937, Rowe<sup>7</sup>, Tufts<sup>23</sup>, Vaughan<sup>25</sup>, and Urbach<sup>24</sup> have considered the question of genito-urinary allergy. Ur-

Read before the American Federation for Clinical Research, Chicago, Illinois, June 12, 1944.

bach, especially, related allergic manifestations to symptoms in different portions of the urinary tract. He supported his thesis with references to experimental evidence and the work of other investigators.

Schultz<sup>18</sup> used strips of sensitized intestinal smooth muscle and found that contact with the specific antigen caused an anaphylactic response with muscular contraction. Dale improved Schultz' technique and developed the uterine strip procedure, which has since become routine in the study of sensitization. The Schultz-Dale reaction of increased contraction of intestinal and uterine smooth muscle is probably the same as the reaction of smooth muscle seen clinically in asthma and urethral and bladder hyperirritability, as well as allergy involving the gastro-intestinal tract. Manwaring<sup>15</sup> and others demonstrated definite uterine and bladder contractions produced by injecting horse serum into previously sensitized dogs.

Discussion as to the advisability of treating pregnant women with pollen hyposensitization arises from the fact that an overdose of pollen extract may produce a reaction in the uterus as a shock tissue. The subject was considered in some detail in the International Correspondence Club of Allergy. Pregnancy, however, is usually no contra-indication to treatment. A similar uterine reaction may be present in certain cases of essential dysmenorrhea. Smith<sup>19</sup> reported twelve cases which responded to allergy management.

Bacterial sensitization occurs in various organs of the genito-urinary tract, especially the kidney. Strong and Fenner<sup>13</sup> perfused kidneys of the tuberculous guinea pig with tuberculin and found marked coagulation and ptosis of the glomeruli and tubules four days later. Controls did not show this change. They also injected tuberculin directly into the kidneys of tuberculous animals and produced necrosis, whereas in the controls the only change was hemorrhage from trauma of the needle.

Bray<sup>4</sup> reported successful relief of enuresis in 100 cases with treatment based on allergy. Patients with associated allergic manifestations such as asthma, hay fever, or eczema were treated for these symptoms as well as for the enuresis. Patients with co-existing conditions which proved to be allergic in origin improved upon removal of the offending allergen. Patients with enuresis *per se* were improved by the removal of an incriminated allergen, although they had failed to respond to the routine management of enuresis. Bray offered evidence in support of the rationale of treatment by drawing an analogy between the nerve supply of the bronchial and vesical musculature. "The analogy between enuresis and allergic conditions in general does not cease with a similarity in innervation of the affected organs. Both conditions tend to recur in bouts with intervals of apparent freedom, both tend to be worse at night, both tend to be accentuated by fatigue or worry, possibly due to sympathetic exhaustion, and both commonly clear up on admittance to hospital."

Vaughan and Hawk<sup>26</sup> reported the case of a medical student, aged



twenty-five, who had recurrent attacks of hydrarthrosis and attacks of renal colic, the latter being promptly relieved by adrenalin. Roentgenograms of the urinary tract showed no abnormal findings. The diagnosis was urinary retention due to urethral obstruction of allergic origin (angioneurotic edema).

In the literature reports may also be found of vaginal discharge with a high eosinophil count<sup>10</sup>, abortions following constitutional reactions to treatment<sup>8</sup>, severe menorrhagia during pollen therapy<sup>20</sup>, pruritus vulvæ during the pollen season<sup>9</sup>, hematuria and purpura with nitrogen retention from sensitivity to onion<sup>1</sup>, constitutional reaction and vaginal bleeding from an overdose of antigen<sup>5,11,12</sup>, and paroxysmal hemoglobinuria in a patient with cold urticaria.<sup>3</sup>

Allergic reactions involving the external genitalia, the vulva, penis, vagina, and anterior urethra, are frequently seen following medication and the use of contraceptives, including creams, jellies, condoms, and so forth. Dermatologic involvement of the genitalia is more closely related to contact factors or agents, which is a subject in itself.

#### DIAGNOSIS

The symptomatology of genito-urinary allergy includes most of the complaints occurring in more common genito-urinary diseases, such as frequency, burning urination, tenesmus, nocturia, enuresis, ureteral colic, dysmenorrhea, leukorrhea, and vulvar irritation. That such symptoms can be allergic in origin is not commonly appreciated, and the cause of such symptoms is often unrecognized.

The diagnosis of genito-urinary allergy depends essentially on an awareness that such a condition may exist. In comparison with pyelitis, cystitis, calculi, and specific infections, genito-urinary allergy is rare, and the diagnosis can be made only after x-ray study, urinalysis, cystoscopy, and other procedures have ruled out the more common causes. In essential hematuria not only must urologic findings be negative, but vitamin C deficiency and purpura must be ruled out before genito-urinary allergy can be considered.

A family history of allergy is also contributory. Complete sensitization studies by scratch and endermal methods should be carried out in an effort to detect the offending allergens. Elimination diets may also be of value.

Eosinophils in the urine are frequently found but not consistently observed in genito-urinary allergy, especially when bladder symptoms are prominent. Relief by the administration of adrenalin is a valuable diagnostic procedure in some cases. Finally, the diagnosis of genito-urinary allergy is made only by exclusion, by therapeutic trial with control of symptoms, and by reproduction of symptoms by subsequent exposure.

## GENITO-URINARY TRACT—THOMAS AND WICKSTEN

### CASE REPORTS

*Case 1.—Hematuria associated with food and inhalant allergy.*—A white man, aged fifty-two, complained of headache and gross hematuria of fifteen months' duration, during which time he had several attacks of severe pain in both flanks. Nocturia had occurred on several occasions, but there was no history of renal calculi nor other genito-urinary symptoms. Repeated urologic investigations failed to explain the hematuria.

While headache was the only personal history of allergy, there was a strong family history of migraine. Laboratory findings were consistent with those to be expected in gross hematuria: red blood cell count was 3,990,000 per cu. cm. with 55 per cent hemoglobin; reticulocyte count was 1.4 per cent; platelet count was 240,000 per cu. mm., coagulation time ten minutes and bleeding time two minutes; prothrombin time nineteen seconds (normal twenty seconds); clot retraction was normal. Cystoscopy revealed gross blood in the urine coming from both ureteral orifices. Catheters were passed to both kidney pelves without resistance. Pyelogram was normal. Sensitization studies showed significant reactions to a number of the common inhalants and molds and to certain foods, including mushroom, squash, pumpkin, canteloupe, cucumber, and watermelon. The patient was advised to remove the offending foods from his diet and to follow a strict inhalant avoidance regimen. Hyposensitization with an extract of house dust, feathers, orris root, and mixed molds was initiated. Within ten days the patient's symptoms subsided, and at the end of four months symptoms had not recurred.

*Case 2.—Frequency and painful urination caused by paint fumes.*—For many years the patient had complained of bladder symptoms such as frequent urination whenever he painted in a closed room. His nasal mucous membranes were also excessively irritated under this condition. Painting out of doors did not produce such symptoms. As a young man he had recurrent hives and developed a sulfur dermatitis while under treatment for scabies. There was a positive family history of allergy. Avoidance of painting within doors or in a closed room controlled his symptoms satisfactorily.

*Case 3.—Dysuria and cystitis from paint fumes.*—A similar case was that of a patient with perennial allergic rhinitis and bronchitis who gave a history of dysuria and cystitis whenever he came in contact with paint fumes. Avoidance was the only treatment necessary for the control of symptoms.

*Case 4.—Frequency and nocturia resulting from food sensitivity.*—A twenty-eight-year-old physician sought allergy consultation for a nasal allergy, allergic conjunctivitis, and recurrent episodes of urinary frequency, nocturia, and dysuria. He believed that his symptoms were aggravated by the ingestion of eggs and beer. As a youth he had recurrent urticaria. His father had a chronic catarrh and a questionable migraine. Positive reactions were obtained from eggs, asparagus, hops, yeast, kidney beans, and coffee. By the elimination of these foods from his diet, his nasal symptoms and conjunctivitis were improved, and his bladder symptoms cleared entirely. Reëxposure would produce recurrence of his ocular, nasal, and bladder symptoms.

*Case 5.—Trigonitis aggravated during an allergic episode.*—In this patient a trigonitis was definitely worse with perennial allergic rhinitis. Many reactions to foods were found by sensitization studies. A complete allergy and urologic survey was made. There was no follow-up.

*Case 6.—Leukorrhea associated with allergic rhinitis.*—A school teacher, aged thirty-nine, complained of intermittent nasal obstruction with watery rhinorrhea

and a profuse mucoid postnasal discharge. The nasal symptoms were perennial and at times were acutely exacerbated. A profuse vaginal discharge was definitely associated with the recurrent nasal symptoms and partially disappeared between attacks.

The nasal mucous membranes were typically allergic with edema, pallor, and watery rhinorrhea. Pelvic examination revealed a whitish vaginal discharge. A 6 per cent eosinophilia was the only significant laboratory finding, and examination of the vaginal secretion during an episode of leukorrhea revealed numerous eosinophils. Sensitization studies revealed significant reactions to many inhalants and to certain foods, primarily eggs and wheat. The nasal symptoms and leukorrhea responded favorably to dietary restrictions, to the avoidance of inhalants, and hyposensitization. The patient voluntarily discontinued her program after four months with the consequent return of her major complaints one month later as severely as before. Treatment was again instituted, and the symptoms were controlled.

*Case 7.—Frequency, tenesmus, and cystitis related to a food allergy.*—A woman in her thirties complained of frequent micturition in attacks recurring at two-week intervals. Symptoms lasted for one day. She said that her bladder felt full and swollen and that she passed considerable urine. She also had allergic rhinitis and bronchial asthma. Corn and celery caused bladder symptoms, and heartburn resulted from the ingestion of lamb, carrots, lettuce, corn, and eggs. The same allergens caused rhinitis. The family history of allergy was very strong. Complete genito-urinary studies were normal. Symptoms were controlled by allergy management.

*Case 8.—Seasonal leukorrhea associated with ragweed hay fever and asthma.*—The patient, aged fifty, gave a history of hay fever, rhinitis, hives, asthma, and vaginal irritation and watery leukorrhea of many years' duration. She was absolutely free of leukorrhea except during the ragweed season. Contact with dust caused rhinorrhea throughout the year. A black silk dress was known to cause hives. The odor of perfume caused spasmodic attacks of rhinitis, which were usually followed by asthma.

She gave positive reactions to scratch tests with ragweed pollen and to conjunctival tests with serial dilutions in carbolyzed saline. A small amount of pollen was applied to the posterior wall of the vagina and observed for 15 minutes; a definite reaction characterized by increased redness and puckering of the mucous membrane was localized to the site of the application, and there was a definite increase in watery discharge from the cervix. Smears showed no eosinophils. The test was observed by a gynecologist, who concurred in the report of the positive and significant reaction. The patient was started on ragweed hyposensitization.

*Case 9.—Uterine spasm as part of a constitutional reaction to preseasonal ragweed treatment.*—A nulliparous young woman with a ten-year history of typical ragweed hay fever had experienced no reaction from previous pollen hyposensitization, which was begun during the winter months. Ten minutes after a dose of 0.45 c.c. of a 1/5000 solution of mixed ragweed extract she developed severe lower abdominal cramps, similar to menstrual cramps. Profuse perspiration, flushing of the skin, and generalized urticaria followed. The reaction was controlled by hypodermic injections of epinephrine, and a tourniquet placed above the site of the injection. The patient's next menstrual period began three days early, and the flow was scanty. The second period was ten days late. After this, however, her menstrual cycle returned to its usual and regular twenty-eight-day cycle. A second constitutional reaction of urticaria followed a dose of 0.3 c.c. of the 1/50 solution of ragweed pollen, but there was no uterine cramping.

## GENITO-URINARY TRACT—THOMAS AND WICKSTEN

*Case 10.—Dysuria and tenesmus following the ingestion of aspirin and acid fruits.*—The patient took aspirin occasionally for severe headache. The drug caused definite burning on voiding, and the amount of urine was reduced. Symptoms lasted twenty-four hours. Acid foods, including citrus fruits, tomatoes, and strawberries caused similar symptoms. No pathologic condition of the urinary tract was found by the urologist.

*Case 11.—Vesical sphincter spasm following the use of ephedrine.*—A white man in the fifties with severe bronchial asthma was given ephedrine for control of symptoms. Each dose of the drug caused spasm of the sphincter and severe bladder discomfort. He voided in small dribbles while under the influence of the drug. Hypodermic administrations of adrenalin were substituted for the ephedrine and produced no symptoms.

*Case 12.—Allergic purpura with associated hematuria precipitated by the inhalation of tar fumes.*—A sixteen-year-old white boy had recurrent hemorrhagic areas in the skin. Six months previously he was exposed to tar fumes in high concentration for two days. The patient had chewed tar frequently as a child. Symptoms appeared four days after exposure and were characterized by severe cramping in the legs, which was followed by nausea, vomiting, and melena. He had repeated attacks of nausea, vomiting, bloody diarrhea, and hematuria. He had swelling of the face and feet, joint pain, occasional hives, and recurrent crops of petechiæ. Pitting and edema were present in the lower extremities, and there was pallor of the skin and profuse sweating. A diagnosis of chronic nephritis was made, and albuminuria persisted for several months. Blood studies were negative.

Allergy studies revealed positive patch tests to crude coal tar ointment. A program of hyposensitization and avoidance of food and inhalant allergens was instituted. Purpuric lesions began to subside after treatment was instituted and did not recur. After nine months of treatment the patient had gained 50 pounds and was in excellent health.

These hemorrhagic tendencies have a mechanism similar to that of anaphylactic shock, characterized by increased capillary permeability, impaired coagulation of blood, and increased permeability of membranes. This is the same type of reaction which Renshaw and Thomas<sup>22</sup> described. By proctoscopic examination they were able to observe congestion and injection of vessels of the rectal mucosa when an allergen was brought in contact with the mucous membrane. The application of ragweed pollen extract to the mucous membrane of a pollen-sensitive patient caused a marked increase in capillary engorgement, even to the extent of rupture and hemorrhage. The absorption of the ragweed pollen was followed by bronchial asthma.

Another patient who complained of seasonal asthma and fall hay fever had severe burning and pruritus of the rectal anus, which was associated with high doses of pollen extract and also occurred in the height of the ragweed season. At one examination mucus was found draining from the rectum. There was no external pruritus ani. The patient showed a 3 plus reaction to a patch test with ragweed.

*Case 13.—Hunter's ulcer with associated hives aggravated by foods.*—This patient developed dysuria five years previously after a four-day attack of generalized hives. Dysuria and frequency of urination were recurrent. Cystoscopy revealed an ulcer near the dome of the bladder. An increase in frequency of urination and dysuria followed the ingestion of chocolate candy or canned grapefruit juice. There was no gross hematuria. She had migraine in 1923 and reported a definite family history of allergy.

The final diagnosis of genito-urinary allergy was based on a questionable allergic

## GENITO-URINARY TRACT—THOMAS AND WICKSTEN

factor in her bladder symptoms, a history of urticaria, and a questionable allergic factor in her headaches. After six weeks' treatment by avoidance of incriminated foods and inhalants and hyposensitization with stock rhinopathogen and enteropathogen vaccines the patient's doctor reported that she appreciated a definite relief from her symptoms.

### TREATMENT

The treatment of genito-urinary allergy, as of any other allergy, is essentially the removal of all offending allergens. Their elimination should be based on complete sensitization studies for foods, inhalants, bacteria, molds, and any other contactants. Foods are the most common offenders, particularly wheat, eggs, and milk, although Rowe has stated that any food may be an offender. The patient should be impressed with the importance of complete elimination of all foods which give positive or even borderline reactions. If results are not obtained by diet based upon sensitization studies, strict elimination diets should be considered. A food diary may be of definite value.

Inhalants may be causative factors, and strict avoidance is imperative. Drugs which may be allergens should be entirely eliminated. Treatment of coexisting allergic manifestations is important. Close co-operation between the urologist and allergist is desirable. Until the symptoms are adequately controlled, sedatives, antispasmodics, anodynes, adrenalin, atropine, and similar drugs may be prescribed for the relief of pain.

### SUMMARY

Allergy definitely must be considered as a cause of genito-urinary symptoms when they cannot be attributed to other causes, when they can be produced at will by the inhalation or ingestion of proven allergens, and when they can be controlled by withdrawal of the allergens. These symptoms may include frequency, painful urination with burning, tenesmus, nocturia, enuresis, ureteral colic, dysmenorrhea, leukorrhea, vulvar and genital irritation, and uterine contractions to the extent of terminating a pregnancy.

The rarity of genito-urinary allergy is understood, and evidence should be carefully weighed before a definite diagnosis is made. The diagnosis is substantiated by other frank allergies in the personal and family history, but it should be made only by exclusion and after therapeutic trial. The cases presented offer substantial evidence of genito-urinary allergy as the explanation of the symptomatology.

The possibility of an allergic reaction in the genito-urinary tract must be considered in the treatment of pregnant women. Reactions to serum or ragweed hyposensitization may cause abortions or premature labor.

Experimental work substantiating the fact that the tissues of the genito-urinary tract manifest a frank allergic or shock reaction is cited.

Close co-operation of the allergist and urologist is necessary if genito-urinary allergy is to be ruled out or, if proved, to be properly managed and results obtained.

## SUMARIO

La alergia debe ser considerada definitivamente como causa de síntomas genitourinarios cuando ellos no se pueden atribuir a otras causas, especialmente cuando se pueden producir a voluntad inhalando o ingestiendo alérgenos conocidos o probados, y también cuando ellos pueden ser reprimidos por el retiro de los alérgenos causantes. En estos síntomas se puede incluir frecuencia, disúria con inflamación, tenesmo, nocturia, enuresis, cólico ureteral, dismenorrea, leucorrea, irritación de la vulva y genitalia, y contracciones del útero hasta el grado de producir un aborto o de terminar la preñez.

La rareza de la alergia genitourinaria es bien sabida y la evidencia debe ser bien examinada antes de llegar a una precisa diagnosis. Se establece la diagnosis por medio de otras manifestaciones alérgicas, en el propio enfermo, existiendo ahora o antes, y también por la presencia de alergia en los antecedentes. Pero, más se hace la diagnosis por medio de la eliminación y los ensayos terapéuticos. Los casos presentados ofrecen una evidencia substancial de alergia genitourinaria como una explicación de la sintomatología.

La posibilidad de una reacción alérgica en la región genitourinaria debe ser considerada en el tratamiento de las mujeres preñadas. Reacciones al suero o a la hiposensibilización de las ambrosias pueden producir abortos o partos prematuros.

Se ha citado el trabajo experimental estableciendo el facto que los tejidos de la región genitourinaria manifiestan una verdadera reacción alérgica o de choque.

Es muy necesario que el alergista y el urologista esten de acuerdo, y que haya una cooperación completa entre ellos, si la existencia de la alergia genitourinaria va a ser considerada. En ella los resultados pueden ser buenos cuando se ha probado que los casos fueron bien estudiados del punto de vista urológico y alérgico.

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(Continued on Page 412)

## CLINICAL EVALUATION OF SOY BEAN FOOD IN ECZEMA OF THE CHILD

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THE care of eczema or atopic dermatitis of the infant and young child always has been a difficult problem. Many papers concerning the disease are on record but there has been a great deal of repetition with an occasional variation when some writers have emphasized certain therapeutic procedures. For many years the eczematous children attending the University and Minneapolis General Hospital allergy clinics have received treatment based on the most popular methods of the day.

The dermatologists have made various contributions to the clinics. Practically all forms of external therapy were tried. However, the response has not been consistent. Some children were observed for a long time and although the eczema appeared to be fairly well controlled, skin manifestations were present until nature decided to clear up the disease spontaneously.

Careful cleansing of the skin, the reduction of trauma by the use of restraints and the administration of sedatives were added to the treatment. Contactants such as wool and silk were avoided. While the results were not satisfactory when fairly large groups of infants and young children with eczema were treated, an occasional case responded well enough to warrant continuation of some form of external therapy.

The pediatricians have urged that the clinic physicians make use of special elimination diets for the cases of eczema. Eggs were removed but this was not enough. Even in those children in which there was evidence that the ingestion of this food had caused flare-ups in the condition of the skin, the elimination of eggs did not lead to a disappearance of the eczema. Milk then was considered as a possible offender. The complete removal of this food from the diet was difficult since it usually constituted a large portion of the daily intake of food for the young child. Rather than eliminating the milk, attempts were made to alter it in such a way that it was less allergenic. First, the milk was boiled and later it was found that it would be simpler to use unsweetened evaporated milk. From this preparation, there was a tendency to drift in the direction of more special preparations, some of which have been referred to as hypoallergic milks. Although these products were not satisfactory in many cases of eczema, enough patients responded favorably to continue the interest in heated milks. Occasionally, goats' milk was employed when the hypoallergic milks failed to produce any

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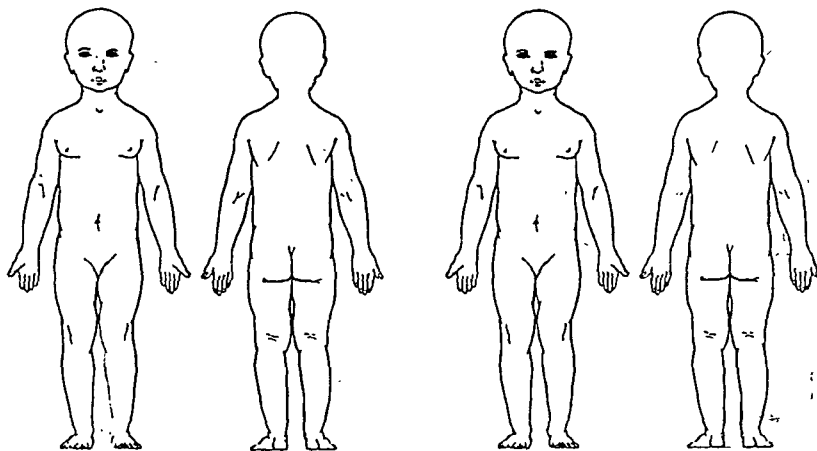
From the Division of Pediatrics of the Minneapolis General Hospital and the Department of Pediatrics of the University of Minnesota Medical School.

# SOY BEAN FOOD—STOESSER

UNIVERSITY OF MINNESOTA  
University of Minnesota Hospitals Department of Pediatrics

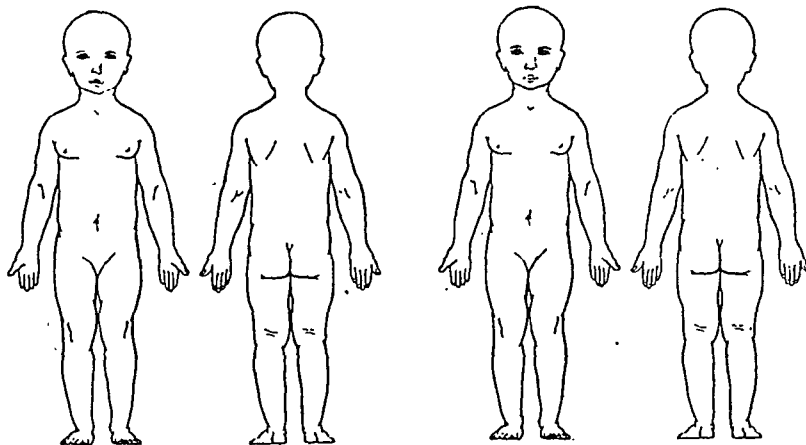
## PROGRESS RECORD OF ECZEMA CASES \*

Case No. \_\_\_\_\_ Name \_\_\_\_\_ Age \_\_\_\_\_ Sex \_\_\_\_\_ Diagnosis \_\_\_\_\_



Date \_\_\_\_\_ Examiner \_\_\_\_\_

Date \_\_\_\_\_ Examiner \_\_\_\_\_



Date \_\_\_\_\_ Examiner \_\_\_\_\_

Date \_\_\_\_\_ Examiner \_\_\_\_\_

KEY: C, crusts; E, erythema; P, pustules; S, seborrhea; T, thickening; V, vesicles; W, weeping;

\* Designed by Dr. Arild E. Hansen, University of Texas.

### CHART I

improvement. The response was good and most interesting was the observation that after the eczema improved with the use of goats' milk, the return to cows' milk promptly led to an increase in symptoms.

For a short period of time a preparation containing meat and vegetable proteins was given to infants and young children with eczema in place of milk. There were some good results but reactions did occur. However, the plan to use a vegetable protein was a good one and suggested the use of a milk substitute made entirely from a vegetable. It was found that soy bean furnished in suitable concentration all the amino



# SOY BEAN FOOD—STOESSER

UNIVERSITY OF MINNESOTA HOSPITALS		Department of Pediatrics		PROGRESS RECORD OF ECZEMA CASES												
Case No.	Name	Age	Sex	Diagnosis												
Clinical data		Date:														
Location	Scalp															
	Face															
	Neck															
	Ears															
	Chest															
	Back															
	Arms															
	Hands															
	Cubital folds															
	Legs															
	Popliteal folds															
	Buttocks															
	Lesions	Seborrhea														
		Erythema														
		Edema														
Vesicles																
Weeping																
Papules																
Only																
Crusts																
Thickening																
Scaly																
Dry																
Pustules																
Impetiginous																
Itching																
Miscellaneous																

KEY: ☐ mild ☐ moderate ☒ severe

CHART II

acids needed for continued normal nutrition. Two preparations made from the soy bean became available. One was in the form of a powder, the other was a thoroughly homogenized emulsion in which the soy bean ingredients and soy bean oil were held in suspension. The former was tried but many infants refused to take it and the product was discontinued. The liquid form was more palatable when properly diluted and an initial trial period showed that the majority of the eczematous infants would take it.

A review of the literature then was made and it revealed little in the way of careful clinical studies concerning the value of soy bean foods in allergic infants and young children. Therefore, a plan was developed which included a close observation of a group of allergy clinic patients with eczema who received a soy bean food as a milk substitute. The examination of the children, the regulation of the treatment, and the recording on special Charts I and II of the results from therapy were performed by the same group of individuals.

A great effort was made to keep everything as constant as possible. The patients were admitted to the hospital and kept in the so-called clean section of the children's ward. A form of isolation technique was carried out in order to prevent as much as possible the introduction of any respiratory infection. When improvement was satisfactory, the cases were discharged and followed in the allergy clinics. Some of

## SOY BEAN FOOD—STOESSER

TABLE I. AGE INCIDENCE AS TO THE TIME OF ONSET OF THE ECZEMA IN 29 INFANTS AND CHILDREN\* RECEIVING A SOY BEAN FORMULA

AGE	No.
2 to 6 mos. (incl.).....	7
7 to 12 mos. (incl.).....	11
13 to 18 mos. (incl.).....	5
19 to 24 mos. (incl.).....	6
Total.....	29

\*There were 22 males and 7 females.

the homes were visited in order to make sure the parents were following all orders correctly.

Up to the present time thirty-seven infants and young children with eczema have been chosen for study. Eight of these cases had to be dropped because they were unable to take the soy bean food. The investigations concerning the remaining children have covered the last two years. The patients ranged in age from two months to two years at the time of their first visit, and age incidence as to time of onset of the disease is shown in Table I. The males predominated.

All of the cases had family histories positive for allergic diseases. The true picture of eczema existed in each child. The skin showed a papulo-vesicular eruption and vesicles formed which ruptured and exuded a yellowish material leading to crust formation. There was scratching giving rise to a punctiform appearance. In fifteen of the twenty-nine children who were finally investigated, there was an associated seborrheic dermatitis with yellow and greasy scales in eight patients and white and dry scales in seven cases, the latter resembling a form of ichthyosis.

The children of the study received a more or less routine form of external therapy which previously had given the best results in spite of the fact that these were not satisfactory. All scalp lesions of the patients with seborrheic dermatitis were well controlled with boric acid ointment (U.S.P.). The face was treated with wet packs of a saturated solution of boric acid or a solution of aluminum acetate (Burow's solution N.F.) diluted ten to twenty times with distilled water. These packs were used for 24 to 48 hours and if necessary were applied to other parts of the body as well as to the face. Following this, an ointment composed of one part of liquor alumini acetatis, two parts of aquaphor (eucerite)\* and three parts of zinc paste was employed. It was gently applied to the skin for a period of three to five days at the end of which time one per cent crude coal tar was added and the application of the latter preparation was continued for approximately one week. Usually by this time the skin was ready for more or less continuous use

\*Made up of a group of esters of cholesterol isolated from wool fat and incorporated in pure neutral chemically indifferent aliphatic hydrocarbons.

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of a preparation consisting of one per cent crude coal tar in equal parts of aquaphor and zinc paste. A few patients had a reoccurrence of the more severe symptoms and the external treatment had to be repeated from the beginning. The cases who appeared to be sensitive to tar pro-

TABLE II.

	Soy Bean Food* Diluted With Equal Volume of Water	Average Whole Cows' Milk
Calories per fluid ounce	20	20
Protein	3.1 per cent	3.3 per cent
Fat	4.0 per cent	3.8 per cent
Iodine No.	119-135	26-28
Carbohydrate	1.0 per cent	4.9 per cent
Total minerals	4.5 per cent	0.7 per cent
Calcium	0.13 %	0.118 %
Phosphorus	0.11 %	0.093 %
Iron	0.0002%	0.0002%
Water	87.2 per cent	87.3 per cent

\*Mull-Soy prepared and furnished by the Prescription Products Division of the Borden Company.

gressed favorably with the use of mixtures of aquaphor and zinc paste.

Trauma was reduced by placing the child on washed X-ray film, employing cuffs on the arms, and restraining both arms and legs if necessary. At feeding time, however, the child was taken up into the nurse's lap and fed in the upright position. If sedation was necessary, phenobarbital was administered in  $\frac{1}{8}$  to  $\frac{1}{4}$  grain doses as often as every four hours during the day until the itching and associated scratching were fairly well controlled. Acute flare-ups of irritability usually were checked with the rectal administration of five to fifteen grains of chloral hydrate.

Little difficulty was encountered in avoiding contact with wool, silk, feathers and kapok.

Soon after the external treatment was started in each case, a special diet was ordered. Since most of the children had been receiving unsweetened evaporated milk with marked variations in the solid foods, the soy bean food, the analysis of which is revealed in Table II, was introduced with a more uniform type of elimination diet. Eggs were omitted completely. Depending upon the age of the child, all cereals were permitted with the exception of those containing wheat. Two cases were clearly demonstrated to have oatmeal sensitivity. All vegetables exclusive of potato, tomato and spinach were added. Occasionally there was some indication of a sensitivity to beans and peas. All cooked fruits and very ripe bananas were given. Any flare-up in the eczematous condition was carefully checked with the recent addition of a new vegetable

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or fruit to the diet. Meats were permitted when the child was ready for them. Fruit juices were omitted and at least 25 mg. of ascorbic acid was administered each day. Drisdol, viosterol, or Oleum Percomorphum in viosterol were employed.

TABLE III. LENGTH OF PERIOD REQUIRED TO OBTAIN SATISFACTORY RESULTS\*

TIME	No.
2 wks. to 1 mo. (incl.).....	8
5 wks. to 2 mos. (incl.).....	11
9 wks. to 3 mos. (incl.).....	6
13 wks. to 4 mos. (incl.).....	2
Over 4 mos.....	2
Total.....	29

\*Eczema disappeared in 18 and was much improved in 11 cases.

The soy bean formula first was prepared by diluting one part of it with two parts of water. After one week, the mixture was changed to equal parts. Eight children referred to before could not take the soy bean formula. They either refused it or developed vomiting, cramps and diarrhea leading almost at once to irritability with an increase in allergic symptoms. Three of the patients had positive cutaneous tests to a soy bean extract; the remaining cases did not give clear reactions. These children have been added to another study involving the use of soy bean oil which is now in progress.

The majority of the patients ingested the soy bean food fairly well. The stools became large and there was a tendency for them to be looser and more frequent than with the ingestion of evaporated milk. In fact in fourteen cases the stools were almost too watery and too many in number to permit continuation of the soy bean product. This situation, however, was remedied by the addition of a kaolin-pectate mixture to the diet in doses varying from one to three drams three to four times each day as long as necessary. No evidence of sensitivity to soy bean protein could be detected in the children developing diarrhea. Could it be due to the fact that soy bean is not digested as easily as other proteins such as meat, whole egg and cows' milk? Four normal non-allergic controls fed relatively large amounts of soy bean formula had large and frequent bowel movements but no diarrhea.

All the patients receiving the soy bean food progressed remarkably well and many were satisfactorily clear of symptoms in a relatively short period of time, as is shown in Table III. This improvement continued and the observation was the most hopeful feature of the study. Twelve of the cases were found to be sensitive to cows' milk by the simple procedure of substituting an evaporated milk mixture of the same caloric

\*The Hormel Institute of the University of Minnesota report on the Review of the Literature on the Nutritive Value of Soy Beans.

## SOY BEAN FOOD—STOESSER

value as the soy bean formula. All other conditions as to external treatment and diet were kept constant. Flare-ups in the eczema occurred in these 12 children and they were returned to the soy bean food following which there was rapid improvement. This procedure was re-

TABLE IV. SOY BEAN FOOD INVESTIGATION

I. Eczema cases chosen for study.....	37
1. Refused to take food.....	8
2. Accepted food (2 mos. to 2 yrs.).....	29
Cows' milk sensitivity demonstrated.....	12
Multiple sensitivities suspected.....	17
3. Developed diarrhea but food not discontinued.....	14
4. Marked beneficial effect from food.....	4
II. Normal control cases observed.....	4
Soy bean food well taken with no diarrhea.	

peated with the same results. Only five of the patients gave positive cutaneous tests to cows' milk protein.

The remaining seventeen cases did not demonstrate any clear-cut reactions to cows' milk in spite of the fact that progress was more satisfactory as long as the soy bean food was employed. Later it was observed that these children could be returned to cows' milk provided small amounts of unsweetened evaporated milk were used. More of the solid foods were permitted but none of the patients could take too rapid an addition of the foods without showing some increase in symptoms. Four children revealed an interesting incident. They had been found to be definitely sensitive to wheat, potato, tomato, or oranges, but after weeks of the ingestion of the soy bean formula, these foods could be eaten with little reaction. When the soy bean food was discontinued and evaporated milk was substituted or no milk was given, the sensitivity to the wheat and the other allergens returned. Members of the group making observations in this study came to the same conclusion after separate checkups of the data collected. No explanation for this phenomenon can be offered at this time but it certainly will be considered an important part of the future fundamental studies which are in progress.

A review of the present soy bean food investigation is presented in Table IV.

### SUMMARY

1. The various forms of external treatment for eczema of the infant and young child have not given results which are consistently satisfactory.

2. The addition of elimination diets to the care of the eczematous children has led to more favorable results, but there still is room for improvement.

3. Combining a good form of external treatment with a more or less uniform type of elimination diet has given the clinical investigator an opportunity to determine the value of special forms of therapy.

4. An investigation has been undertaken with a soy bean formula. All factors have been kept as constant as possible in order to make a careful observation of the influence of this food on the course of the eczema.

5. The study has been a difficult one. Thirty-seven children were offered the soy bean formula. Eight could not take it and soy bean sensitivity was only suspected in three of these patients. Twenty-nine cases ranging in age from two months to two years ingested the food very well, but fourteen developed a diarrhea which was controlled. Four normal non-allergic controls receiving the soy bean formula did not have diarrhea.

6. All of the children progressed remarkably well, with eighteen revealing good, and eleven fairly good, results in a relatively short period of time. The improvement continued long enough to make this observation quite significant.

7. Twelve of the patients were found sensitive to milk. The remaining seventeen were considered to be sensitive to more than one food. Four of the latter showed an interesting phenomenon. Apparently after weeks of soy bean food ingestion, they were able to tolerate much better the other foods to which they had given clinical evidence of sensitivity. This warrants more study.

#### CONCLUSIONS

When external treatment of the skin is of the best and a good elimination diet is employed, a soy bean food can produce a beneficial effect in eczema of infants and children both in the milk-sensitive patients and in the multiple-food-sensitive cases.

All children cannot take the soy bean formula. Some refuse it and others have gastro-intestinal symptoms indicating a possible allergic reaction. Almost one-half of the patients develop a diarrhea but fortunately in most cases this can be controlled.

#### RESUMEN

1. Las varias formas del tratamiento local en el eczema de los lactantes y niños no han dado todavía resultados que sean suficientemente satisfactorios.

2. La adición de las dietas de eliminación para mejorar el eczema de los niños, ha mostrado resultados más favorables, pero aun no es suficiente.

3. La combinación de un buen tratamiento local con una dieta de eliminación del tipo más o menos uniforme, ha dado al investigador clínico una oportunidad para determinar la terapéutica necesaria.

4. Una investigación ha sido hecha con la formula del Soy Bean. Todos los factores han sido cuidados constantemente como para hacer una observación cuidadosa de la influencia de este alimento en el curso del eczema.

5. Este estudio ha sido difícil. 37 niños fueron tratados con la fórmula del Soy Bean. 8 de ellos no pudieron tolerarlo. Solamente en 3 de ellos la sensibilización al Soy Bean fué sospechosa. 29 de estos casos, entre dos meses a dos años de edad toleraron el alimento muy bien, pero 14 de ellos mostraron una diarrea la cual fué controlada por nosotros. 4 individuos normales, no-alérgicos, tratados como control, toleraron perfectamente la fórmula del Soy Bean sin mostrar diarrea alguna.

6. Todos los niños progresaron remarcablemente bien, 18 mostraron un resultado bueno, y en 11 el resultado fué regular, en un período de tiempo relativamente corto. La mejoría continuó por un tiempo suficientemente largo como para considerar esta observación como un buen resultado.

7. Se encontró que 12 de los enfermos eran sensibles a la leche. En el resto, que fueron 17, se encontró que eran sensibles a más de un alimento. En 4 de estos últimos se observó un interesante fenómeno. Aparentemente después de la ingestión del Soy Bean por algunas semanas, pudieron tolerar mucho mejor los otros alimentos a los cuales tenían una evidente sensibilidad clínica. Esto necesita mayor estudio.

### Allergy in Relation to the Genito-Urinary Tract

(Continued from Page 403)

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## THE ALLERGIC PROBLEM OF THE INDUCTEE, THE SOLDIER, AND THE VETERAN

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EVERY medical examiner of the Draft Board is concerned with the question of allergy each time he examines a registrant for induction. How am I to know if this registrant is suffering from any allergic disease? He knows well the difficulty encountered, that is, once the allergic sufferer is free from symptoms, he behaves again like a normal person. He also knows well that several of these registrants are eager to see active military service, and would not reveal the fact that they are suffering from one or more allergic diseases.

Assume he has mentioned that he has bronchial asthma or hay fever, how is the examiner going to evaluate the degree of the severity of the allergic symptoms? He should ask the following questions: (1) Is asthma or hay fever or any of the other allied conditions present in the immediate or remote members of the family? (2) Have you any definite knowledge that the partaking of certain foods causes any of the following symptoms: diarrhea, belching, nausea, vomiting, hives, sick headaches, visual disturbances, rhinitis, abdominal colic, swelling of the face or extremities? (3) Have you any knowledge that when you handle furs or animals of any sort, or go horseback riding you develop a heavy feeling in the chest with shortness of breath and running nose or sneezing? To the female registrant put this question: (4) After going to the beautician for a hair wave or hair setting, or after using hair lotions of any kind, do you develop periodically sneezing, running eyes, running nose, heaviness in the chest with a sensation of oppression, or eruptions of different varieties? Finally ask these registrants this last question: (5) Do you get frequent attacks of "colds," sinus infection, sore throat, and are these conditions present throughout the year or only through special seasons of the year?

If to the first question the registrant replies, "Yes, Doctor, I have a brother with asthma," the statement strengthens the possibility that the examiner may be dealing with a potentially allergic individual, or one already suffering from some form of an allergic manifestation. He knows that an allergic disease like bronchial asthma or hay fever is not directly inherited, but that the tendency is directly inherited.

If to the second question the registrant answers, "Yes," the examiner should ask more definite questions. What particular foods actually cause these already mentioned symptoms and how soon after eating do these symptoms appear?

If to the third question the answer is "Yes," the examiner can assume with a degree of certainty that this applicant is sensitive to the danders or epithelia of certain animals, whether domestic or not.



If to the fourth question the applicant answers "Yes," the examiner surmises that ingredients like flaxseed, orris root, cottonseed, and others are undoubtedly the offending agents, and that he is presumably dealing with an allergic individual.

If the last question is answered in the affirmative, the examiner knows he is dealing with either chronic infection or with a definite periodical form of sensitivity which may be either hay fever or perennial vasomotor rhinitis or allergic rhinitis.

It is a well-known fact that many persons still do not know specifically that there are such diseases as bronchial asthma, hay fever and allergic rhinitis. To them, spells of coughing or shortness of breath are nothing but a long cough or bronchitis, to which they don't pay much attention. Others think that the rhinorrhea or itching of the eyes causing tears is nothing but just an ordinary "cold," which at times lasts a little longer. They call them just "summer colds." The data concerning the symptoms as related by the registrant are very important. He may say, "Well, Doctor, occasionally, I have just a little tightness in the chest, shortness of breath, a little wheezing and a very slight cough." This order of sequence should lead the examiner to think that he has before him a prospective asthmatic, who most probably has not yet developed asthmatic attacks of appreciable severity. If he simply says, "Doctor, I have a little cough at first, then I may get slightly short of breath and wheeze a little," the examiner can assume with a great degree of certainty that he is dealing with an individual suffering from bronchitis of the asthmatic type. This, however, is by no means a hard and fast rule in all cases.

Let us assume, now, that the registrant has definitely admitted he has asthma. How is the examiner then going to make the diagnosis that either bronchitis, alone, or bronchitis with pulmonary emphysema is present along with the asthma? He should ask this question, "How long have you had asthma?" This is important because the duration of the disease often gives a clue as to the type of allergy to expect, the possible prognosis, and the possibility of complications. For instance, summer asthma may mean pollen, seasonal foods, or other types of seasonal exposure, such as fly emanations, horseback riding and so on. Attacks of asthma in the wintertime may mean bronchial infections, cold sensitivity or more close exposure to house allergens. Another important question to ask is this, "Are you free or are there any symptoms, between attacks?" If there is no shortness of breath, cough, or general ill-health between attacks, most likely no complications have developed. However, if the registrant says he coughs a great deal every day between attacks, the examiner should consider that bronchitis has set in. If he says that he brings up a great deal of phlegm with the cough, the examiner should suspect the presence of bronchiectasis. If there is a history that marked dyspnea or exertion is present between attacks, then emphysema, pulmonary, is most likely present. If he says, "Doctor, I have 'colds' that

last a very long time," allergic rhinitis and sinusitis should be considered. Here again the history of allergy in the family strengthens the diagnosis that one is dealing with an allergic person. The story of dermatitis or the so often loosely called eczema and hyperesthetic rhinitis, which have now disappeared, or the history of having had any other allergic manifestations in the past, is more likely in favor of an allergic character of the asthma. Some applicants will say, "Well, Doctor, I had pneumonia a year ago and following it, I developed a cough which is persistent but not disturbing at present." They will add, "I cough occasionally, particularly after I catch a 'cold' or after a little 'grippe.' I don't get any attacks of asthma whatsoever." These statements are more in favor of "asthmatic bronchitis."

The examination of the prospective inductee should be thorough, particularly when bronchial asthma is suspected. Inspection, as a rule, does not reveal anything characteristic about the general physique of the asthmatic person. The asthmatic sufferer with emphysema, however, has a chest which tends to take the shape of a barrel. The ribs are elevated. The individual with intractable asthma is a little easier to detect. He usually looks thin. This is really because of the continued nutritional deficiency produced by the chronicity of this disease.

If the applicant is examined during an attack of asthma the diagnosis is very easy. His breathing is rapid and shallow and wheezing noises are usually heard at considerable distance from him. This is an important observation. When he inspires, there is very little expansion of his chest and yet the chest looks enlarged. He breathes really by elevating the entire thoracic cavity with the aid of the accessory muscles of respiration. The neck muscles are usually prominent and the veins in the neck look engorged. The applicant usually keeps on coughing during the examination. On percussion of the chest, it is found that the entire thoracic cavity, as a rule, is hyperresonant, especially during the asthmatic attack. The area of cardiac dullness may be obliterated. Auscultation reveals a variety of râles scattered throughout the chest. They are usually dry. They are described by many as sibilant or sonorous, but the appropriate term is really "wheezing râle." As a rule, since these râles are generalized, they quite frequently obscure any other auscultatory changes which may be present in the chest. The nasal mucous membrane may show a definite edema in some cases, but not in all.

If the applicant presents himself for examination when he is free from symptoms of asthma, the examination should include the following: (1) nose and throat; (2) teeth; (3) cardiovascular system; and (4) laboratory and roentgenographic examination of the chest and sinuses.

The direct nose and throat examination may show varying degrees of these findings: blanched, swollen mucous membrane; boggy blanched inferior and middle turbinates; and a thin discharge or rhinitis. This is particularly seen in the hay-fever and allergic rhinitis persons. Transillu-

mination should be part of the examination of these applicants with an allergic history. This examination should be followed by a roentgenogram of the sinuses of the head and face.

The examination of the teeth is, as a rule, performed routinely in all applicants. If, however, infected roots are present they should be marked and extracted as soon as possible after their induction. These foci of infection may be responsible for the precipitation of an attack of asthma or may be foci for other diseases.

The examination of the chest in an applicant who is free from attacks of asthma usually does not show very much, but if this applicant has been getting frequent attacks, the examiner will find a few wheezing râles. These can be best elicited by compression of his chest manually, immediately following a forced expiration. In this examination he should look for the possible presence of other disease processes resembling asthma or the further complications of this disease. If emphysema is present, the chest is usually increased in diameter, especially antero-posteriorly. The expansion of the chest is diminished. The apices and the bases are usually more hyperresonant than normal. There is very little excursion of the apices and the bases during a full deep inspiration. The breath sounds are diminished in intensity and the expiratory phase is prolonged.

If moist râles are heard, then bronchitis should be considered. If constant localized moist râles are heard in the bases or lower portion of the lung field, bronchiectasis should be considered. In advanced cases, there may be present dullness and diminished breath sounds.

In the examination of the cardiovascular system of the chronic asthmatic, the following conditions are present: The blood pressure is usually low, and there is marked change in the pressure between expirations and inspirations. The heart is usually within normal limits, except when pulmonary hypertension has set in. There are usually no arrhythmias or murmurs present. The tones of the cardiac sounds are feeble. When the applicant is free from symptoms of asthma there are usually no deviations from the normal.

In the laboratory examination of the bronchial asthmatic person, the most constant microscopic finding is the presence of a large number of eosinophiles in the sputum and nasal secretion, and at times in the blood. This finding is more noticeable during an attack of asthma. Many bacteria are usually present in the sputum, like the non-hemolytic streptococci, micrococcus catarrhalis, pneumococcus, staphylococcus and other bacteria. In the differential count of the blood, one should look for eosinophiles. There is usually an eosinophilia of 4 to 10 per cent and sometimes higher. The other laboratory methods, including electrocardiographic tracings, as a rule do not show very much.

Roentgenographic examination of the chest should be routine. This, however, is done not for the diagnosis of asthma, which usually is negative, but for the detection of any complications and the presence of

other diseases simulating asthma, and also for the discovery of unrelated chest diseases. During an attack of asthma, fluoroscopy and roentgenography show that the lungs are distended and there is very little expansion. During the interval free from symptoms, there may be present hylum enlargement and increased bronchial markings. If it shows very heavy shadows, bronchiectasis is suspected. This, however, is best diagnosed with iodized oil. This last method should be in the hands of the expert who has considerable experience with its use. The other conditions to be looked for are atelectasis, tuberculosis, pneumonitis, new growth and other chest conditions.

It should be routine practice of every examiner to subject every applicant with a positive familial history of allergy, to skin tests. The method of choice is left to the examiner. He can use the method with which he is most familiar. The intracutaneous method, however, seems to give the best results. If the registrant so tested is found sensitive with marked reactions to some of the inhalants or air-borne substances, he should be considered either as a potential allergic, or as one who already has some form of allergic manifestation, even though the physical examination has been negative. The tests should include all available materials which may have a reasonable bearing on the symptoms.

Colonel Sanford W. French, MC, and Major Lawrence Halpin, MC<sup>1</sup> have written an excellent paper entitled "Report of Allergy in the Fourth Service Command." This paper is really the first of its kind to give a detailed description of the allergic problems as encountered in the Army. I quote directly from the paper:

"Most of the hay-fever patients dated the original onset of their complaint many years prior to their induction into the Army. A few, however, denied any previous complaints of this character. The discomfort and the severity of symptoms in these patients were sufficient to interfere with the performance of their duties. . . . Institution of pollen therapy and continuation of that therapy in the out-patient clinic permitted these patients to perform full duty throughout the rest of the season."

This shows that hay-fever symptoms are controllable if proper treatment is instituted early. These authors bring out these important points in the summary:

"In a summary of twenty-one clinics, 3,419 Army allergy patients and 498 civilian allergy patients were reported to the Surgeon General's Office. From January to October, 1942, 1,153 allergy patients were admitted to the hospitals of these twenty-one stations. . . . The average hospital days were eighteen."

Those allergic soldiers whose symptoms of asthma or other allied conditions are well controlled with proper treatment and who are able to perform their duties as a soldier are kept in the Service. Those, however, with severe symptoms which render them very disabled are given a certificate of disability discharge (CDD).

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Some of the allergic soldiers who have been given a certificate of disability discharge feel they have a grievance against the Army medical officer, because they believe the medical officer has been directly responsible for their discharge from the service. They also feel that the Service is responsible for all ailments from which they may be suffering. The Army records, however, show that every one of them receives excellent medical and general attention.

This soldier, who is now back again in civilian life with an honorable discharge, is known as a veteran. He soon learns he is entitled to benefits for service-connected disabilities, and nonservice-connected diseases or injuries. Through his contact officer, either in the American Legion, or in the Veterans of Foreign Wars organization, he learns he is entitled to three kinds of veterans' benefits, namely: (1) monetary benefits, including disability compensation, pension, adjusted compensation, and Government insurance; (2) hospitalization, or domiciliary care, and out-patient treatment; and lastly (3) burial and funeral expenses. This latter, of course, is of very remote interest.

For those who are not familiar with the Veterans' Administration, it is worthy of mention. The main office of this organization is located in the Veterans' Administration Building, Washington, D. C. Over 100 field stations are located in the various states, and there are insular offices in Hawaii, the Philippines, and Puerto Rico. The managers of all field stations are responsible to the Administrator in Central Office. The stations are classified as follows: (1) Veterans' Administration regional offices, whose principal functions are administrative; (2) Veterans' Administration facilities, which have regional office functions in addition to hospital and domiciliary activities; (3) Veterans' Administration facilities having major domiciliary activities with hospital accommodations; (4) Veterans' Administration having only hospital activities; and (5) Veterans' Administration facilities having regional office functions in addition to hospital activities.

The principal functions of the regional offices are: (1) Contacts with and assistance to claimants and beneficiaries or their representatives as provided by law; (2) preparation and adjudication of claims for disability compensation and pension of persons whose entire military or naval service was subsequent to July 15, 1903, and prior to October 8, 1940; unless jurisdiction is otherwise vested in central office; (3) guardianship activities for incompetent beneficiaries; (4) making of medical examinations; (5) rendering out-patient relief—surgical, dental and prosthetic—to veterans not patients in a Veterans' facility; (6) adjudication of claims for burial and funeral expenses.

After this veteran has obtained all the necessary information from his contact officer, he places a claim on a special form No. 526, namely, "Application for Compensation for Veterans' Disabilities in World Wars I and II.

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For those who are not acquainted with the work of the Veterans' Administration, particularly the medical side, it is well to mention here that there are two separate divisions, the medical division and the adjudication division. Each one is supervised by two separate directors. The physicians working for the medical division are known as medical officers, and those working for the adjudication division are known as medical rating specialists. Their duties differ a great deal.

Those physicians who accept positions in the adjudication division are assigned to a training course at a designated facility for a period of four to six weeks.

The medical officers designated to make examinations for rating purposes must also be specially trained. The medical examiner must know that the medical rating specialist is really concerned with the reflecting pictures of functional impairment, as can be translated into percentage evaluations of average reduction in earning capacity from such injuries or diseases in civil occupations. It is really the relative disability resulting from the disease or injury about which the medical rating specialist is concerned. A clear full report of the expressions of disability, that is, the physical findings and the subjective symptomatology, is needed.

The difference between compensation and pension should be mentioned here. Compensation is a term used to describe the monetary benefits payable on account of service-connected death or disability resulting from service in World War I. Corresponding benefits payable on account of service other than World War I are termed "pensions." The latter term is also used to describe nonservice-connected monetary benefits, including those payable to World War II veterans.

Since the amount payable to a veteran is in accordance with the degree of disability attributable to service, not existing prior to induction or aggravated by service, it is important then to describe all the symptoms and findings properly and in the proper sequence where practicable.

Most of the diseases are rated in terms of degree of severity, from *mild* to *moderate* and *severe* symptoms. Bronchial asthma, as an example, is rated as follows:

*Asthma, mild* is rated as such when the symptoms or attacks occur at widely separated intervals, and when there is no pulmonary emphysema present. A veteran given such a diagnosis and rated as such by the Medical Rating Board receives a rating of 0 or no per cent.

*Asthma, moderate* is rated as such when the attacks are rather frequent (ten- to fourteen-day intervals), and when there is slight to moderate amount of emphysema, with moderate dyspnea between the attacks. A veteran given such diagnosis and rated as such by the Medical Rating Board receives a rating of 30 per cent.

*Asthma, severe* is rated as such when the attacks are very frequent, and when there is moderate to severe dyspnea with continuous emphysema between the attacks, and also when there is embarrassment of heart action.

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A veteran given such diagnosis and rated as such by the Medical Rating Board receives a rating of 50 per cent.

If the above symptoms, as in severe asthma, are accompanied with dyspnea at rest, and cyanosis with severe impairment of general health or total disablement, the asthma is rated as 100 per cent.

All the above ratings are according to the 1933 schedule. There is a 1925 schedule also.

The other diseases and injuries are rated practically in the same manner. The important thing to remember is to describe the subjective and objective symptoms and findings properly, not to forget the laboratory and x-ray examinations when indicated. The medical examiner is not to modify the disease or injury by the terms *mild*, *moderate* or *severe*. This should be left to the medical rating specialist and other members of the Rating Board. They are the ones who will use these modified terms after the respective diagnoses.

Once a veteran has been given a rating for his service-connected disease of disability by the Medical Rating Board, whether directly incurred in service or aggravated by service, he is informed about it in writing. Thereafter, he receives the allotted sum every month regularly. If the diagnosis given is of a temporary nature—that is, the condition may improve or get worse, he is called for re-examination after a period of eighteen months or earlier. At present there are thousands of veterans with service-connected diseases or injuries who are receiving out-patient and in-patient treatment in Veterans' hospitals and domiciliary facilities. This number has already grown tremendously. The need for more Veterans' hospitals is certainly becoming very urgent, particularly now with the incoming of hundreds of new veterans daily from World War II.

The medical officers of the Veterans' Administration have great tasks ahead of them to perform. They know that every case can be followed from the day of the veteran's induction in military service until his last days. The veteran knows he has an excellently equipped hospital at his command with various specialists on whom he can call for consultation. It is the opinion of this writer that as the Administration grows, there will be a need for more full-time medical officers, and specialists on full-time and part-time basis. The aim of the Administration is to give the veteran the best medical attention at its command.

So far, there are several diagnostic centers of all sorts in the Administration, but as for allergy, there is only one such center in the country, namely, in Pittsburgh, Pennsylvania, and, unfortunately, situated in the most unhealthy place in the country for allergic patients. The director of this allergy center feels there is a growing need of other such centers in different parts of the United States, which we all hope will be formed soon. These places should act not only as diagnostic allergy centers, but also as centers of learning, giving intensive courses in allergy to medical officers interested in this field.

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So far a great deal has been said about the claimant whose claim has been granted for compensation or pension, but nothing has been said about the other veteran whose claim has been denied. What recourse is then open to this claimant? He may appeal from a decision rendered by the Rating Board, provided the appeal is taken within one year; otherwise the decision becomes final. The appeal application must be signed by the claimant or his accredited representative, and must contain alleged mistakes of facts or error of law in the adjudication of the claim. It is important to mention this here. The ratings of disability are usually made upon a liberal basis and consistent with the facts in every case. When, after a careful consideration of all procurable and assembled data, a reasonable doubt arises regarding service origin, the degree of disability, or any other point, such doubt is usually resolved in favor of the claimant.

A veteran whose claim has been denied for service-connected or service aggravation, even after appeal, is still entitled to hospital treatment, providing, of course, he has received an honorable discharge from the last period of war service, and also if he makes a statement under oath that he is financially unable to supply himself with the necessary hospital treatment, and also providing a bed is available. This veteran so hospitalized for whatever allergic disease, may receive in addition to medical treatment other benefits, like toilet articles, smoking tobacco or cigarettes, stationery and postage, barber service, providing his income is less than \$6.00 monthly. He may also receive personal clothing when his monthly income is less than \$10.00.

When a veteran is hospitalized in a Veterans' Administration facility, he receives all the necessary medical care. The allergic patient receives a thorough allergic study. Later when he is discharged from the hospital, a summary of all the findings and also directions about treatment in the future are sent to his family physician, providing he gives such authorization in writing.

The same veteran and any other veteran is eligible to domiciliary care also if he or she has not been dishonorably discharged from his or her last period of war service and is unable to defray the expense of such care. This form of treatment is granted when he or she is suffering from a disability, disease or injury (defect) that incapacitates him or her from earning a living for a prospective period of time.

Vocational training is available also to all veterans who have been in active military service anytime after December 6, 1941, and during the present war, providing they have received an honorable discharge, and have disability or disabilities incurred in or aggravated by such service for which a pension is payable under laws administered by the Veterans' Administration or would be but for receipt of retirement pay, and are in need of vocational training to overcome the handicaps such disability or disabilities. During authorized training, pension is payable at the rate of \$80 per month to a single man and \$90.00 to a married man, with an



## INDUCTEE, SOLDIER, VETERAN—SHAHON

added allotment of \$5.00 per month for each dependent child and \$10.00 per month for each dependent parent.

When one considers all the benefits that an honorably discharged veteran is entitled to, he immediately realizes that, after all, it is worth fighting for Uncle Sam.

### SUMMARY

1. The difficulties encountered by the examining physician of the Induction Board are discussed.

2. The important questions for the detection of the allergic manifestations in prospective soldiers are pointed out.

3. The allergic problem as encountered in the Army is briefly mentioned.

4. The benefits that honorably discharged veterans receive are amply discussed.

5. This question is still debatable, namely: How is the Rating Board specialist going to know whether the allergic disease existed prior to induction or enlistment? If at the time of such examination, the examiner finds that the physical examination is negative and that the history does not suggest the existence of allergy in the family, and the allergic tests if performed are negative, then it is safe to assume that the allergic disease or manifestation was not there at that time. If, later, this soldier develops any allergic disease, it can be said that it developed during service. Later, when this soldier is discharged from service, service connection for such a disability can be given. It is true that allergic diseases are not directly inherited and the tendency alone is inherited, yet no one can foretell the exact time of their appearance in life. As stated before, it is possible that factors like overexertion, worry, exposure to cold or excessive heat, dampness, emotional strain and many others might precipitate the appearance of that hereditary tendency.

If, on the other hand, the allergic disease was present at the time of induction or enlistments to a degree hardly noticeable, and later it became greatly manifested with symptoms so disabling as to cause separation from the Service, it can be said with some degree of certainty that this disease undoubtedly was aggravated by service.

It is hoped that this paper will be of service to the examining physician of the Induction Board, to the medical officer at the enlistment or induction center, and the medical officers of the Armed Forces, to the Medical Board rating specialists, to the medical officers of the Veterans Administration and to all medical practitioners in civilian life.

### SUMARIO

1. Se han discutido las dificultades que el médico del Consejo de Inducción encuentra en el examen físico.

2. Se han apuntado las interrogaciones principales para descubrir las manifestaciones alérgicas en los soldados en perspectiva.

3. Se ha discutido brevemente el problema alérgico según se encuentra en la Armada.

4. Se ha resuelto en detalle los beneficios que reciben los soldados honorablemente licenciados.

5. Este asunto es todavía disputable, especialmente en: ¿Cómo puede saber el especialista del Consejo de Evaluación, si la enfermedad existía antes de la inducción o alistamiento? Si en el momento de este exámen, el médico encuentra que el exámen físico es negativo, que en la historia no hay ninguna sugestión de la existencia de alergia en los antecedentes, y cuando las pruebas cutáneas son negativas, se puede decir, con cierta seguridad, que la enfermedad alérgica o manifestacion no existía en aquella hora. Si más tarde este mismo soldado desarrolla un enfermedad alérgica, se puede decir que ella se ha desarrollado en el Servicio o Armada. Más tarde, cuando este soldado es licenciado ésta enfermedad se puede relacionar al Servicio. Sí es verdad que las enfermedades alérgicas no son directamente heredadas y que la tendencia solo es heredada, ninguno pude pronosticar cuando es el momento exacto de su aparición en la vida. Según ya se ha citado antes, es posible que factores como éstos: esfuerzos excesivos, angustias, contacto con mucho frío o calor, humedad, esfuerzo emocional y muchos otros, pueden precipitar la aparición de esta tendencia hereditaria.

Si, por otra parte, la enfermedad alérgica, existia en el momento de la inducción o alistamiento en un grado casi imperceptible, y más tarde se manifiesta con síntomas que incapacitan al soldado, causando su separación del Servicio, se puede decir, con cierta seguridad, que la enfermedad fué, sin duda, agravada por el Servicio.

Se espera que éste articulo sea de beneficio para el médico del Consejo de Inducción, el médico oficial en el Centro de Inducción o Alistamiento, y los médicos oficiales de las Fuerzas Militares; y también para los especialistas del Consejo Médico de Evaluación, los médicos oficiales de la Administración Veterena, y todos los médicos practicos en la vida civil.

#### REFERENCE

1. French, Sanford W., and Halpin, Lawrence J.: Army allergy. Report on allergy clinics in the Fourth Service Command. *Ann. of Allergy*, 1:1-16 (July-August) 1943.

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UREA FOR MIGRAINE. Brown, J. A.: *Brit. M. J.*, 2:201, (Aug.) 1943.

Attacks of migraine were treated with 20 gr. of urea in water three times a day for one week; 20 gr. twice a day for one week, and 20 gr. daily for an indefinite period. There were no untoward effects. It is felt that the good results may be due to the correction of a temporarily disturbed tolerance by the diuretic action of the urea. The patients' symptoms returned when the therapy was discontinued.

L. J. H.

# EXPERIMENTAL APPROACH TO ORAL TREATMENT OF FOOD ALLERGY

## I. Chemistry of Food Propeptans

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THE role of type-specific propeptans in the diagnosis and treatment of food allergy has been discussed in some detail elsewhere.<sup>1,2</sup> The present paper will be devoted to a discussion of the chemical properties of these propeptans.

Propeptans are derived from the individual foods through digestion by hydrochloric acid, pepsin and trypsin. Thus these preparations contain all the protein cleavage products such as the proteoses, peptones, subpeptones, simple peptids and amino acids. On the other hand, as demonstrated by tests with 10 per cent sulfosalicylic acid and 10 per cent trichloroacetic acid, propeptans do not contain any native protein; nor do they contain metaprotein.

The guiding principle in the preparation of propeptans is to destroy the native protein through mild and partial digestion of the protein, but to preserve its type-specific complexes; the latter, administered in proper doses, are intended to protect the hypersensitive organism against certain food items which would otherwise elicit characteristic allergic manifestations. In order to achieve this goal, hydrolysis is performed with the mildest digestive ferment available, namely pepsin, which promotes this process under optimal pH condition. However, since under the digestive action of pepsin, large complexes of amino acid chains remain intact in molecular form, it is necessary to subject the products to some further, but very slight degradation by trypsin. Yet this latter process must by no means be carried too far, for a too radical splitting of the chains and breaking off of some of the components will result in the destruction of the type-specific complexes and thereby destroy the type-specific action of the preparation.

We have performed an extensive series of animal experiments to determine the conditions under which food digests are most effective. These experiments revealed the fact that the best protective action is given by digests comprising proteose-N (70 to 80 per cent), peptone-N (approximately 10 to 15 per cent), with subpeptones, simple peptides and amino acids making up the balance. Table I shows the great differences in the degree of protein disintegration, depending on the type and strength of the ferment employed and also on the duration of the digestive process.

From the Department of Allergy, Jewish Hospital.  
Expenses for this work were defrayed in part by a grant from the Allergy Research Foundation, Inc., Philadelphia, Pa.

# FOOD ALLERGY—URBACH, ET AL.

TABLE I. COMPARISON OF THE CHEMICAL COMPOSITION OF THE PROTEIN FRACTION OF EGG DIGESTS DEPENDENT ON THE TYPE AND DEGREE OF DIGESTION

	Deep Acid Pepsin Digestion. Then Light Alkaline Trypsin Digestion. Egg Digest No. 16	Deep Acid Pepsin Digestion. Then Moderate Alkaline Trypsin Digestion. Egg Digest No. 15	Deep Acid Pepsin Digestion. Then Deep Alkaline Trypsin Digestion. Egg Digest No. 11
Total N	9.15	7.03	9.30
Water Soluble N	9.15	7.03	9.28
Water Insoluble N	None	None	0.02
Acid Precipitated N	None	None	None
Proteose N	6.90	2.81	2.26
Peptone N	0.89	1.38	3.96
Subpeptone and Simple Peptid N	0.14	1.52	1.62
Amino Acid N	1.22	1.32	1.44
Percentage of Soluble Nitrogen as:			
Proteose	75.3	40.0	24.4
Peptone	9.7	19.6	42.7
Subpeptone and Simple Peptid	1.6	21.6	17.4
Amino Acid	13.4	18.8	15.5

Table I also demonstrates that when only a slight degree of alkaline trypsin digestion supplements the intensive, acid digestion performed by pepsin, the proteose-N comprises nearly four-fifths of the total-N. A moderate degree of digestion by trypsin lowers the proteose-N to 50 per cent and a high degree to some 25 per cent. At the same time, the levels of the deeper cleavage products of the protein increase.

It is almost self-evident that the total N-contents of the various propeptans must be dependent upon the relative abundance of protein in the original substance. They vary to a certain extent, depending on the origin, age, et cetera of the substances from which they are derived. Highest in nitrogen content are egg, meat and fish propeptans; then come peanut, cheese, pea propeptans. Celery, orange and grapefruit propeptans have the lowest nitrogen content.

The various protein cleavage products in the different propeptans are also subject to quantitative fluctuations within certain limits. These fluctuations may be explained primarily by the differences in the ferments employed (their concentration, duration of exposure to the digestive process, et cetera). Moreover, it is quite natural for animal and vegetable products to react differently, within certain limits, to ferments; therefore, special quantitative factors must be considered when dealing with each individual food item. Thus, it is difficult to get as high a percentage of proteose-N from foodstuffs rich in sugar and cellulose, notably fruits and vegetables, as from animal food products. Lastly, before subjecting a given foodstuff to the digestive procedure it should be

# FOOD ALLERGY—URBACH, ET AL.

TABLE II. CHEMICAL COMPOSITION OF SIX REPRESENTATIVE FOOD PROPEPTANS

	Beef	Egg	Wheat	Milk	Carrots	Apple
Total N	11.40	9.15	7.85	4.00	3.26	1.75
Water Soluble N	11.40	9.15	7.85	4.00	3.26	1.75
Water Insoluble N	None	None	None	None	None	None
Acid Precipitated N	None	None	None	None	None	None
Proteose N	8.03	6.90	6.26	2.69	1.87	1.09
Peptone N	2.07	0.89	0.85	0.70	0.22	0.16
Subpeptone and Simple Peptid N	0.15	0.14	0.13	0.29	0.86	0.33
Amino Acid N	1.15	1.22	0.61	0.32	0.31	0.17
Percentage of Soluble Nitrogen as:						
Proteose	70.4	75.3	79.7	67.3	57.2	62.5
Peptone	18.2	9.7	10.8	17.4	6.8	9.3
Subpeptone and Simple Peptid	1.3	1.6	1.7	7.2	26.5	18.7
Amino Acid	10.1	13.4	7.8	8.1	9.5	9.5

TABLE III. COMPARISON BETWEEN PROPEPTANS AND COMMERCIAL PEPTONES

	Beef Propeptan	Armour's Peptonum Siccum	Bacto Peptone	Fairchild's Peptone
Total N	11.40	14.00	14.56	13.60
Water Soluble N	11.40	14.00	14.56	13.60
Water Insoluble N	None	None	None	None
Acid Precipitated N	None	None	Trace	0.10
Proteose N	8.03	6.93	7.41	7.28
Peptone N	2.07	2.41	3.12	1.67
Subpeptone and Simple Peptid N	0.15	1.82	1.37	0.85
Amino Acid N	1.15	2.84	2.66	3.70
Percentage of Soluble Nitrogen as:				
Proteose	70.4	49.5	50.9	53.6
Peptone	18.2	17.2	21.4	12.3
Subpeptone and Simple Peptid	1.3	13.0	9.4	6.3
Amino Acid	10.1	20.3	18.3	27.2

briefly boiled, since raw foodstuffs are generally adulterated with bacteria which may lead to toxic products in the preparation.

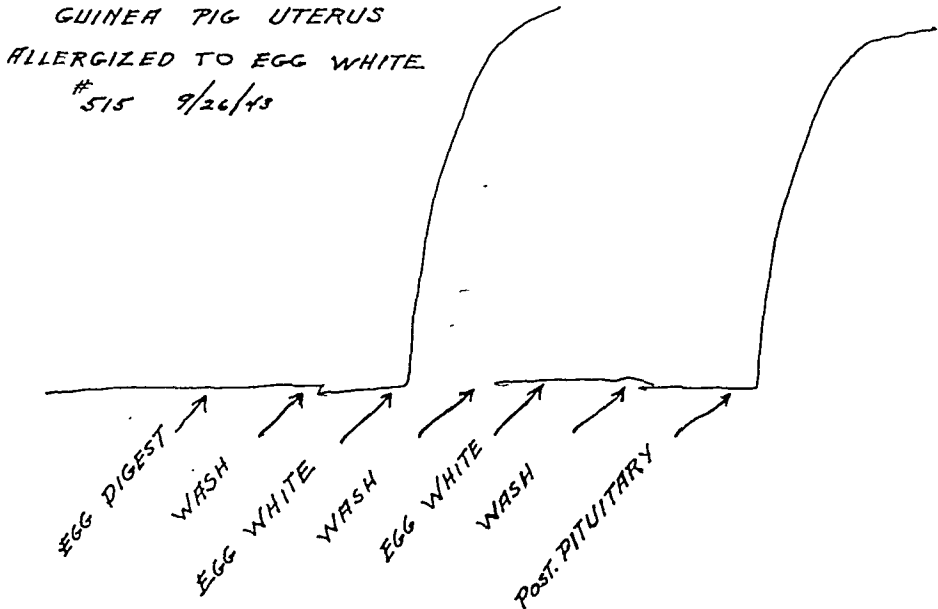
Table II presents a few representative examples.

Table III illustrates the average composition of the propeptans\* as compared, for example, with commercial preparations of protein cleavage

\*We analyzed pure food digests (propeptans), which Dalare Associates were kind enough to put at our disposal. Glycyrrhiza, which in itself contains 1.4% protein, is added to the commercial propeptans. Each food propeptan capsule contains 0.02 g. glycyrrhiza and a small amount of calcium phosphate.

products. It clearly shows that the commercial peptones are degraded far more extensively than the propeptans.

The protein cleavage products were analyzed according to the procedure described by Wasteneys and Borsook.<sup>3</sup>



Graph 1. Schultz-Dale test performed upon the uterus of a guinea pig allergized to egg white and receiving no protective treatment. There was no reaction upon the addition of Egg Digest 16. A violent reaction followed when egg white was added, indicating a high degree of hypersensitiveness. There was no reaction to a second portion of added egg white, proving that the first reaction was specific for egg white. The final reaction was the result of posterior pituitary extract added as a check on the sensitivity of the uterus.

TABLE IV. GUINEA PIG 510 ALLERGIZED TO EGG WHITE; TREATED BY INTRAVENOUS INJECTIONS OF EGG DIGEST 16; FOLLOWED BY SHOCK DOSES OF EGG WHITE

Allergized by intraperitoneal injection of 0.1 c.c. of 50 per cent Egg White in Saline. 9/23/43.  
Treatment: By intravenous injections every ten minutes.

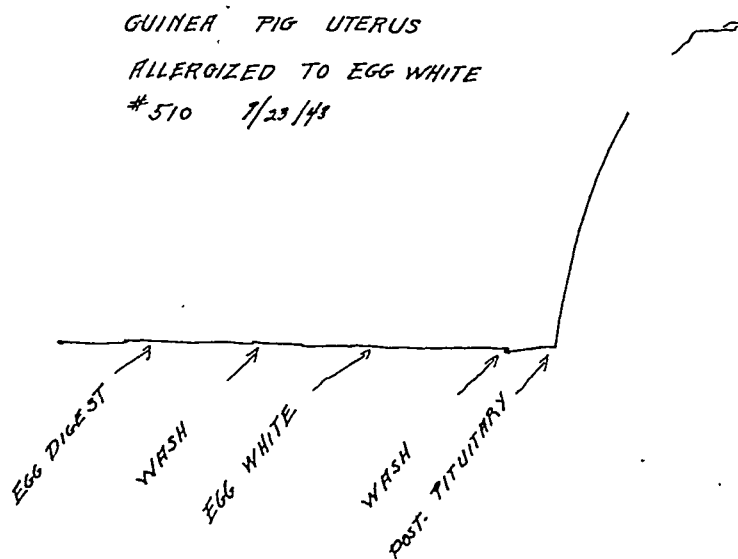
Dose	Soluble Nitrogen of Egg Digest 16	Reaction
1	1.0 mgs.	None
2	2.5 mgs.	None
3	5.0 mgs.	None
4	10.0 mgs.	None
5	20.0 mgs.	None

Fifteen minutes later—Shock Doses of Egg White every five minutes.  
1 M.L.D. = 0.1 c.c. of 1 per cent Egg White (0.02 mg. of soluble Nitrogen)

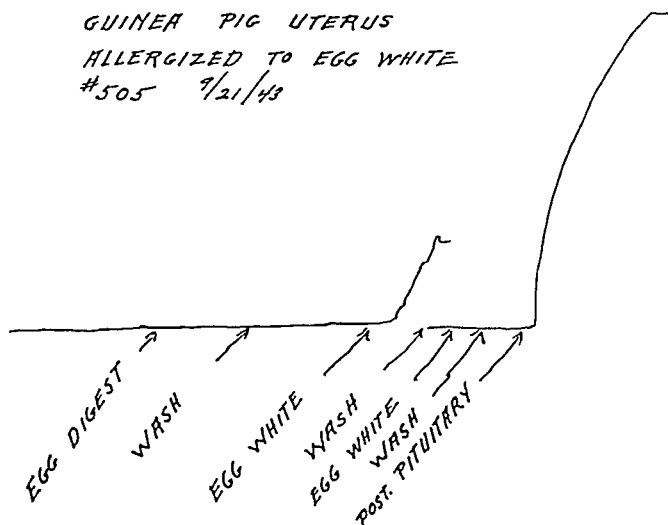
Shock Dose	M.L.D.	Reaction
1	1	None.
2	2.5	None.
3	5.0	None.
4	10.0	Slight, bristling.
5	20.0	Slight, bristling. Animal was killed by blow on head forty-five minutes after the last shock dose.

In addition to chemical analyses we have endeavored to study the problem of optimum amounts of digestion of food proteins by the anaphylactic experiment. The following tables and graphs show that clinical protection and de-allergization as demonstrated by the absence of an-

tibodies from the uterus, can be achieved only when the propeptans retain their type-specificity or, in other words, if the degradation of the protein is not carried too far.



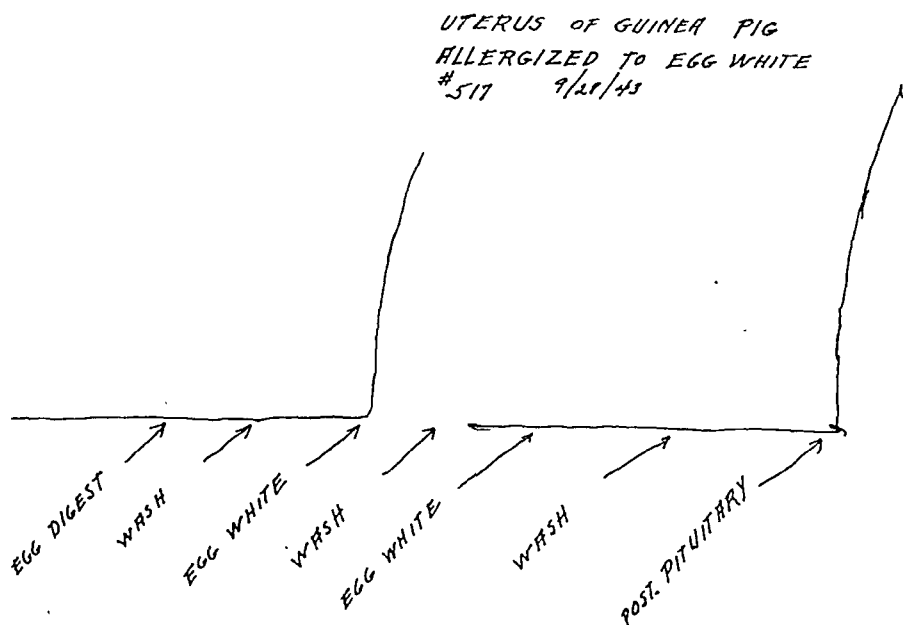
Graph 2. Schultz-Dale test performed upon the uterus of a guinea pig allergized to egg white, followed by parenteral skeptophylactic treatment with Egg Digest 16. There was no reaction upon the addition of Egg Digest 16, and no reaction upon the addition of egg white, indicating absence of antibodies in the uterus. Posterior pituitary extract was added as a check upon the sensitivity of the uterus.



Graph 3. Schultz-Dale test performed upon the uterus of a guinea pig allergized to egg white, followed by parenteral skeptophylactic treatment with Egg Digest 15. There was no reaction upon the addition of Egg Digest 15. A slight reaction followed upon the addition of egg white, showing that some but not all of the antibodies have been neutralized by the treatment. No reaction to a second portion of added egg white indicated that the reaction was specific. A final addition of posterior pituitary extract was made as a check upon the sensitivity of the uterus.

As mentioned above, Table I presents the analyses of three digests of egg, subjected to various degrees of degradation with enzymes.

Graph 1 illustrates the violent reactivity of the uterus of a guinea pig that has been allergized to egg and not been protected with Egg Digest 16. The reaction was elicited by adding egg extract.



Graph 4. Schultz-Dale test performed upon the uterus of a guinea pig allergized to egg white followed by parenteral skeptophylactic treatment with Egg Digest 11. There was no reaction upon the addition of Egg Digest 11. A violent reaction followed the addition of egg white, indicating the presence of considerable quantities of antibodies. No reaction followed a second addition of egg white, proving that the preceding reaction was specific. A final addition of posterior pituitary extract was made as a check upon the sensitivity of the uterus.

TABLE V. GUINEA PIG 517 ALLERGIZED TO EGG WHITE; TREATED BY INTRA-  
VENOUS INJECTIONS OF EGG DIGEST 11; FOLLOWED BY A  
SHOCK DOSE OF EGG WHITE

Allergized by intraperitoneal injection of 0.1 c.c. of 50 per cent Egg White in Saline. 9/28/43.  
Treatment: Intravenous injections at intervals of ten minutes.

Dose	10% Egg Digest 11	Soluble Nitrogen	Reaction
1	0.1 c.c.	1.0 mg.	None
2	0.25 c.c.	2.5 mg.	None
3	0.50 c.c.	5.0 mg.	None
4	1.00 c.c.	10.0 mg.	None
5	2.00 c.c.	20.0 mg.	None

Fifteen minutes after last treatment

Shock Doses of Egg White every five minutes.

1 M.L.D. = 0.1 c.c. of 1 per cent Egg White (0.02 mgs. of Soluble Nitrogen).

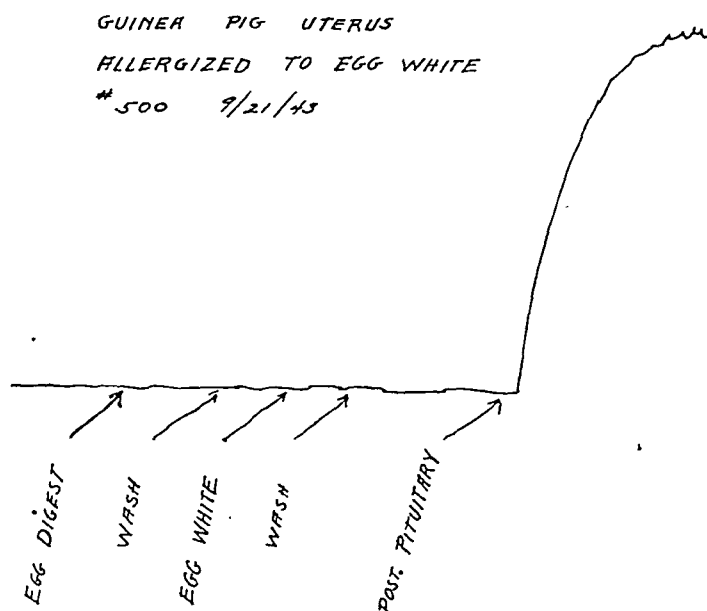
Shock Dose—1 M.L.D.—Animal died in six minutes in severe anaphylactic shock.

Table IV and Graph 2 demonstrate that parenteral skeptophylactic treatment with Egg Digest No. 16, consisting of about 75 per cent proteoses and 10 per cent peptones, protects the guinea pig against 20 minimal lethal doses and deallergizes the animal, as shown by the complete absence of antibodies from the uterus.

Digest 15, which is composed of approximately 40 per cent proteoses and 20 per cent peptones, gave less satisfactory clinical results; moreover, the uterus reacted slightly to egg white (Graph 3). However, when



the protein is too deeply digested, as demonstrated by the chemical analysis, the quantity of peptones (42.7 per cent) almost double that of proteoses (24.4 per cent), one minimal lethal dose will suffice to kill the



Graph 5. Schultz-Dale test performed upon the uterus of a guinea pig allergized to egg white, followed by an oral treatment with Egg Digest 16. There was no reaction upon the addition of Egg Digest 16. No reaction followed the addition of egg white, indicating the absence of antibodies in the uterus. Posterior pituitary extract was added as a check upon the sensitivity of the uterus.

TABLE VI. GUINEA PIG 500 ALLERGIZED TO EGG WHITE; TREATED BY ORAL ADMINISTRATION OF EGG DIGEST 16; FOLLOWED BY SHOCK DOSES OF EGG WHITE

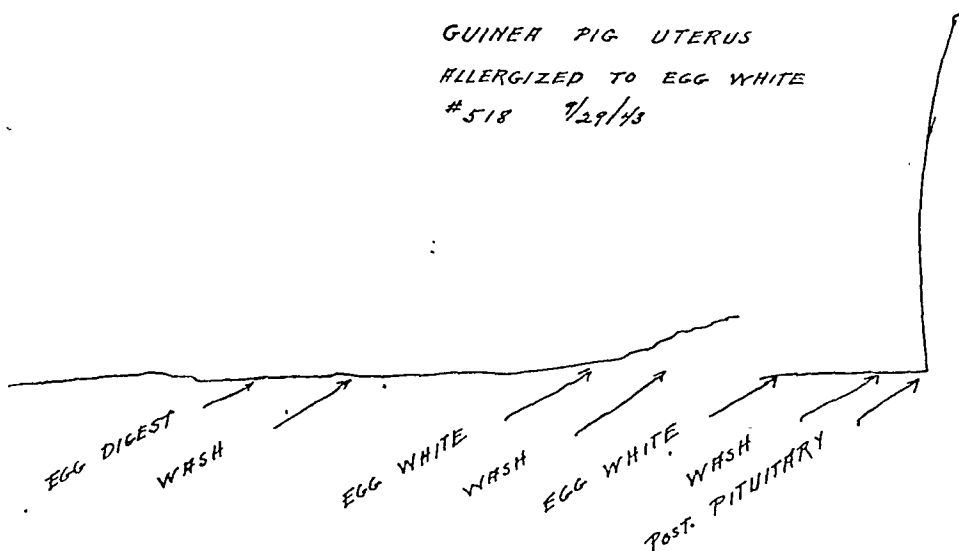
Allergized by intraperitoneal injection of 0.1 c.c. of 50 per cent Egg White in Saline 9/21/43.  
Treatment: By mouth, 5 mgs. of Soluble Nitrogen of Egg Digest 16 + 0.2 grams of Glycyrrhiza + 2.0 c.c. of water.  
Sixty-six hours later—Shock Doses of Egg White every five minutes.  
1 M.L.D. = 0.1 c.c. of 1 per cent Egg White (0.02 mg of Soluble Nitrogen).

Shock Dose	M.L.D.	
1	1	None.
2	2.5	None.
3	5.0	None.
4	10.0	Slight twitching of nose and bristling.
5	20.0	Slight, bristling, but fully recovered in one hour. Then killed by blow upon head.

animal (Table V) and the uterus will react violently, proving that it contains considerable quantities of antibodies. (Graph 4).

Virtually identical results were achieved when the propeptans were administered orally. In contradistinction to the intravenous skeptophylactic technique, which consisted in giving five doses of the digest and the lethal shock doses immediately thereafter, the oral technique called for administration of the digest in one single dose, sixty-six hours prior to the injection of the allergen. Egg Digest 16, given orally sixty-six hours before administration of the doses, gave the animals protection against the 20 M.L.D. Only a very mild reaction, in the form of brist-

ling, was observed. The uterus was found to be free from antibodies (Table VI, Graph 5).



Graph 6. Schultz-Dale test performed upon the uterus of a guinea pig allergized to egg white and followed by an oral treatment with Egg Digest 15. There was no reaction upon the addition of Egg Digest 15. A slight reaction followed the addition of egg white, indicating that many of the antibodies were neutralized by the treatment. Posterior pituitary extract was added as a check upon the sensitivity of the uterus.

TABLE VII. GUINEA PIG 518 ALLERGIIZED TO EGG WHITE TREATED BY ORAL ADMINISTRATION OF EGG DIGEST 15; FOLLOWED BY SHOCK DOSES OF EGG WHITE

Allergized by intraperitoneal injection of 0.1 c.c. of 50 per cent Egg White in Saline 9/21/43.  
Treatment: By mouth, 5 mgs. of Soluble Nitrogen of Egg Digest 15 + 0.2 grams of Glycyrrhiza + 2.0 c.c. of water.

Sixty-six hours later—Shock Doses of Egg White every five minutes.

1 M.L.D. = 0.1 c.c. of 1 per cent Egg White (0.02 mg of Soluble Nitrogen).

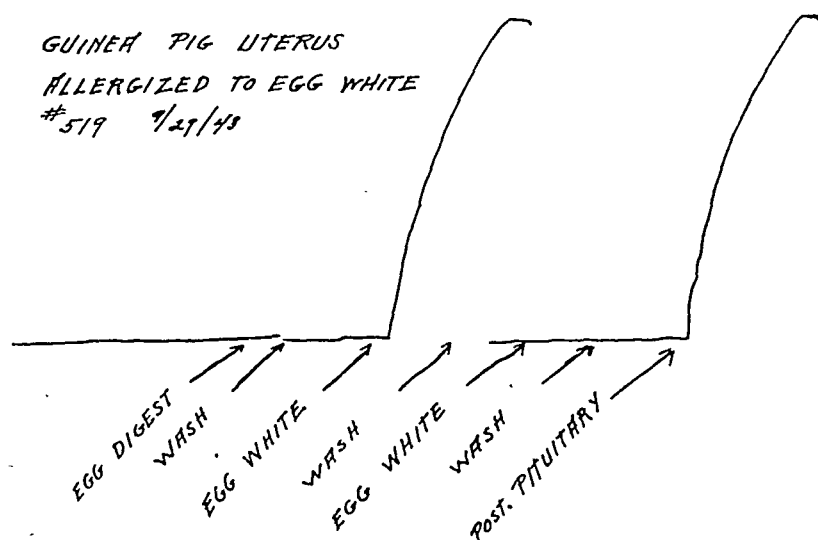
Shock Dose	M.L.D.	
1	1	None.
2	2.5	None.
3	5.0	Slight, twitching of nose.
4	10.0	Marked, gasping.
5	20.0	Animal died in twenty-five minutes.

Egg Digest 15, given orally, gave adequate protection against 5 M.L.D., but 20 M.L.D. were fatal (Table VII). The uterus contained a fair amount of antibodies, as evidenced by the slowly-rising curve in the Schultz-Dale experiment (Graph 6).

Egg Digest 11, given orally, did not even afford protection against 1 M.L.D. (Table VIII; the uterus, correspondingly, reacted violently to egg white (Graph 7).

In conclusion, we wish to state that experiments with the oral approach further confirm and definitely highlight the value of food proteins that have been subjected to only a mild degree of degradation. While these animals which were pretreated with Digest 16 tolerated 20 M.L.D. very well, guinea pigs receiving Digest 15 became markedly anaphylactic when

10, M.L.D. were injected, and died, following 1 M.L.D., if Digest 11 was used.



Graph 7. Schultz-Dale test performed upon the uterus of a guinea pig allergized to egg white, followed by an oral treatment with Egg Digest 11. There was no reaction following the addition of Egg Digest 11. A violent reaction followed the addition of egg white, indicated the presence of considerable quantities of antibodies. No reaction followed a second addition of egg white proved that the preceding reaction was specific. A final addition of posterior pituitary extract was made as a check upon the sensitivity of the uterus.

TABLE VIII. GUINEA PIG 519 ALLERGIZED TO EGG WHITE; TREATED BY ORAL ADMINISTRATION OF EGG DIGEST 11; FOLLOWED BY SHOCK DOSE OF EGG WHITE

Intraperitoneal injections of 0.1 c.c. of 50 per cent Egg White in Saline.  
Treatment: By mouth, 5 mgs. of Soluble Nitrogen Digest 11 + 0.2 grams of Glycyrrhiza + 2.0 water.  
Sixty-six hours later  
Shock Dose 1 M.L.D. of Egg White = 0.1 c.c. of 1 per cent Egg White (0.02 mg. soluble nitrogen).  
Shock Dose—1 M.L.D.—Animal died in six minutes with anaphylactic symptoms.

#### SUMMARY

Food propeptans are food digests derived from the individual foods through prolonged digestion with hydrochloric acid and pepsin, followed by some slight additional digestion with trypsin. While these preparations are devoid of any native protein, they contain type-specific proteoses and peptones which have the capacity of giving highly-sensitized animals full protection against anaphylactic shock.

#### SUMARIO

Los alimentos propeptonas son alimentos digestivos derivados de alimentos individuos después de una digestión prolongada con ácido hidrolórico y pepsina y seguida por una digestión adicional lijera en pepsina. Mientrás estas preparaciones no contienen ninguna cantidad de proteína

(Continued on Page 439)

## ALLERGY IN MEXICO

MARIO SALAZAR MALLEN, M.D., F.A.C.A. (Hon.)  
Mexico City

I WISH to express my sincere admiration for the endeavors of the founders of the American College of Allergists in setting forth measures to unite all those interested in the advance of medicine and allergy. I also wish to convey my deep appreciation to the American scientists whose contributions have given to this country an outstanding and well-deserved place in science in general and medicine in particular. We know that the benefits of scientific research in medicine have no frontiers, and I am certain that the advances made in your clinics, universities and laboratories will reach humanity, their ultimate goal.

To talk of "Allergy in Mexico" does not mean that I shall show you the oddities seen after having practiced for eight years privately and as chief of the only free clinic devoted to the study of allergic patients. Neither shall I insist upon giving figures, percentages or tables to enlarge upon what I and my associates have encountered in our people. Allergy in Mexico cannot be very different from what it is in Colorado or La Habana, and there are only those local peculiarities which you very well know.

To begin with, I can state that allergic diseases are very common in my country, since a city of around two million inhabitants has within a small interval of time given me the opportunity of diagnosing some 3,000 cases, mostly sufferers of "major allergies." Of this figure, 1,000 belong to the charity clinic at the General Hospital where there is a constant demand for more diagnosis and treatment than we can provide, owing to the lack of sufficient personnel and facilities for clinical examination. I am pretty certain that in the very near future, the opening of our new unit devoted to nutrition and allergy will give us a pronounced increase in this type of patient.

It was, and still is, claimed that high altitudes do not produce asthmatics, but we see in Mexico City at some 7,000 feet above sea level many asthmatic sufferers of the allergic, infectious and intrinsic type. The material studied privately gives the distribution in relation with diagnosis of the different allergic syndromes shown in Table I.

Some authorities have stated that our latitudes and altitude make the pollinosis unimportant. I have also read that ragweed does not flourish in the valley of Mexico. This statement must be challenged, and I think that you all will be interested to know that pollens do exist in the air of Mexico City and also that ragweed (short) is seen shedding pollen everywhere in field or yards from July to September. It must be explained, however, that our ragweed pollinates when the rainy season is heavy, and therefore we never have recorded more than 25 grains per square centimeter a day (we still find practical the sedimentation counts).

## ALLERGY IN MEXICO—MALLÉN

TABLE I. MAIN ALLERGIC COMPLAINTS IN PATIENTS SEEN IN PRIVATE  
PRACTICE (1,687 Cases)

Respiratory allergy (includes vasomotor rhinitis, allergic cough and bronchial asthma) .....	1027	(62%)
Pollinosis .....	104	
Urticaria (includes angioneurotic edema and other allergic erythemas).....	300	(17%)
Eczema and other forms of allergic dermatitis.....	207	(12%)
Migraine (includes other allergic headaches, nervous symptoms and histaminic headache) 97		( 5%)
Gastro-intestinal allergy (as main complaint).....	56	(2.5%)

During the dry wintertime, the cedar tree (*Cupressus Benthami*) sheds an important amount of pollen, but the most significant and troublesome irritant at this season is ash (*fraxinus vir.*), since this tree adorns our parks and important avenues and streets. Pollen of green ash is seen from the beginning of November, not disappearing until the end of February. Counts reach as high as 100 grains per square centimeter a day or more.

In the valley of Mexico, these might be considered the most vexatious plants, but Bermuda grass is so widespread from very early March to the middle of August with its pollen grains seen in rather scarce amounts (from 2 to 10 grains) that cases with long and very bad symptoms are also encountered.

Cosmos and sunflower cause symptoms during the autumn and a few persons have positive reactions related to the floral characteristics of the seasons to *Amaranthus retroflexus*, alder, oak and rye grass. We have plantain, poplars and willows, but their season is rather short, and I have not seen patients with symptoms originating from these latter. Australian pine and true pine shed huge amounts of pollen, but so far, I believe as do many of our American colleagues that casuarinæ and pine tree are not very allergenic plants. Local flora, such as *schinus molle* and cactaceae, do have pollen but this is not transported through the air, and I have never had occasion to be suspicious of them. The following table records the cases of pollinosis seen in the Republic of Mexico and in inhabitants of Mexico City itself (Table II).

More important in our asthma and coriza cases is dust; we do encounter plenty of pure dust and associate dust cases. Feathers are also important and once in a while offer the pleasant surprise of being the only offender. Orris root is also significant; less so, other epidermals and miscellaneous.

Foods as causes of respiratory symptoms are of utmost importance. Secondary to dust many cases react cutaneously and clinically as food sensitives, the main offenders being cereals, the most important of which is corn, followed by wheat and rice. I seldom see oats or barley or buckwheat cases, but of course you well know the reason; corn is vastly used as food among us; it is the foundation of enchiladas, tortillas and other dishes less known to you, but it is and always has been our favorite food staple. Rice is also a favorite, whereas bread occupies a less significant place in our diet. Rye and buckwheat are rarely consumed, so they are not important. Following the cereals in importance, we have chocolate, peanuts and meats. Milk is troublous, but eggs are far from being important

# ALLERGY IN MEXICO—MALLÉN

TABLE II. POLLENS AS CAUSES OF ALLERGIC (RESPIRATORY) SYMPTOMS

Pollen	Cases	From Mexico City	Other States
Bermuda grass	37	26	Nuevo Leon Coahuila Chihuahua Sonora Sinaloa &
Ragweed (short)	36	20	Nuevo Leon Tamaulipas Sonora Sinaloa Oaxaca Michoacan
Johnson grass	16	none	Coahuila Chihuahua Sonora Sinaloa Jalisco
Green ash	14	14	
Pigweed	7	none	Sonora Sinaloa Michoacan
Russian thistle	4	none	Chihuahua Nuevo Leon Sonora
Cedar tree (Cupressus b.)	3	3	
Other pollens: Slender ragweed False ragweed Cosmos Sunflower	12	7	Sinaloa Sonora Tamaulipas Chihuahua

allergens. Vegetables are significant as secondary offenders, and beans (frijoles) have a well deserved place in exciting allergic symptoms as well as large and even general reactions. Our native fruits, with the exception of the mango, do not seem to cause trouble. Our fruit cases are usually nuts, orange, lemon and banana.

Bacterial symptoms are indeed found, especially giving origin to acute asthmatic and status asthmaticus symptoms, but sinusitis does not seem to be so widespread in our patients.

We do see spores in our slides and test our patients with alternaria, hormodendrom, fusarium, rhizopus, candida, aspergillus and mucorinea. Reactions are seen, and some patients seem to improve when spore extracts are applied to them.

Outside of Mexico the respiratory allergy changes in a noteworthy way: asthma and pollinosis are very prominent factors in our border and Pacific Coast states. Allergens are local; most of the patients improve after coming higher to our plateaus or even removing from the Pacific coast. The first are more likely simple pollinosis, such as Johnson grass, timothy, Bermuda grass, Russian thistle, Amaranthus, slender ragweed, false ragweed. Many other allergenic plants must exist in the fields of our north-western states, but we are still awaiting the opportunity of securing co-operation for making a botanical survey. The second type of patient who improves only upon getting away from the seashore would seem to offer

evidence that the ocean climate is the cause of symptoms present. He is a different problem, as he usually fails to show sensitivity to pollens, is slightly sensitive to dusts and gets no results from dust treatment. Following the studies of Jimenez' Diaz, we believe that asthmatics from the coast may be sensitive to fungi, but our own fungi extracts have not yet solved the problem. Patients from the Gulf coast have interesting features; some from the northern part are truly sensitive to pollens of local importance such as short ragweed or Bermuda grass, but many belong to cities along the seashore or inhabit towns inside the coast itself which are characterized by being damp and hot. Patients from these latter places often complain of feeling the barometric fall and of getting invariably worse when north winds blow and the sky is clouded. I have visited some of the very asthmogenic localities with this type of patient and have been impressed by the many sufferers with the above characteristic who suffer only if they remain in their own localities. The allergenic flora of these places includes Bermuda, Rumex and some compositae, but patients fail to react to any of them. Fungi have been suspected of being the cause of trouble among these sufferers and some results have been obtained with local fungi. Mucorinea and Aspergillus, in particular, encourage research along this line.

Skin allergy occupies second place in its frequency in our material, urticaria and dermatitis running parallel. Contact dermatitis is seldom seen, probably because these cases remain in the hands of our able dermatologists. Urticaria, however, is always labelled allergic, and the allergist himself is often requested to find the allergen. With Dr. Taboada I have reported our experience with this nightmare of allergists. Even though we were far from identifying the causes of our patient's symptoms, we accepted a clinical distinction between our allergic, toxic and infectious cases. In practice, we believe to be allergic the patient who shows urticaria along with other allergic traits, and we consider it worth while to test him. Our toxic cases are so named if the basis of the skin symptoms seem to reside inside the body and particularly if we can find a near or remote cause of changes in the intestinal flora with or without prominent intestinal symptoms. We label infectious urticarias those which have infectious foci such as gall bladder, appendix, teeth or tonsils which might be incriminated of either sensitizing or, less likely, intoxicating the patients. Allergic urticarias tend to be paroxysmal and associated with other allergies. Infectious and toxic urticarias may be of the "intrinsic" type, but the first are connected with cholecystitis, sore throat and so on, and the latter we relate to not very obvious intestinal changes. This classification is only clinical and for clinical use. We are still waiting for a better understanding of common hives.

Dermatitis flexuralis is seen, as a rule, in atopic people. Contrary to the opinion of some authorities, we do consider it worth while to test them, and in our very limited experience the allergic investigation of these patients produced gratifying results. "Ids" are indeed seen! fungides are

very common in hot weather; other microbids are much rarer, but not absent.

Circumscribed neurodermatitis is not frequent, but presents considerable difficulties in its causal diagnosis except in cases of associated allergies.

Even though morphology may be typical of certain "ids," allergies or parasitic dermatosis, we do not consider that a given localization excludes the existence of different or associated factors.

Migraine, nervous and gastro-intestinal symptoms are also often observed, but I do not deem interesting a résumé of details that are well known to you. Migraine is often allergic, but psychosomatic symptoms play an outstanding role. I have seen interesting cases of cerebral symptoms related to allergy associated with urticaria and migraine, which cleared nicely upon testing and eliminating the offending foods.

My experience is limited in allergic purpuras or other allergic symptoms.

In relation to treatment, very few points deserve consideration, since our methods are not fundamentally different compared with yours.

Allergic patients are treated specifically whenever feasible, and good results are obtained by hyposensitizing with dusts and pollens. Results are less encouraging by injecting specific foods, but hyposensitization is always tried. Stubborn cases of asthma suspected of being purely intrinsic or bacterially intrinsic, after failure of diets and other general measures, receive roentgen therapy which gives satisfactory results to an important percentage of patients.

Nonspecific treatment of respiratory allergy is often used by injecting histamine and/or peptone by the intramuscular route; both drugs produce evident improvement to the allergic patient with exceptional undesirable side reactions. Tuberculin therapy is not a favorite procedure since our first attempts with its use did not convince us of its effectiveness.

Symptomatically we apply sympathomimetic drugs and, following the work of the continental authors, use ephyllin either orally or intravenously.

Skin allergies are treated topically whenever possible (dermatitis); infectious urticarias are handled when possible by treatment of the source of symptoms or by the cautious use of autogenous or heterogenous vaccines; toxic (intestinal) urticaria receives histamine treatment, and recently sulfasuxidine and other bacteriostatics.

Migraine seems to improve tremendously if the specific allergen is found and suppressed, otherwise there seems to be no drug available for its cure, and psychotherapy is resorted to in selected cases.

In closing, I wish to stress the importance of submitting to our colleagues of the College, our common experiences in the management of the allergic patient, and after constructive discussion I am certain that better understanding of our common problems will result in progress in treatment.



# Editorial

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## OLD AGE SECURITY

We who are growing old in the field of allergy are beginning to feel the need of security as we are pushed by the young fellows coming up. Allergy is practiced by men of many stages of maturity, many degrees of skill, and that is as it should be. The thing that every society must watch is that the control of it does not pass into the hands of those who want security above everything else, who place prestige above service. When this happens, then these leaders will draw like-minded men to themselves to bask in the reflected glory of the society which they have founded.

As we have outlined in a previous editorial,<sup>†</sup> there is room for all the organizations now concerning themselves with allergy in America. There is no overlapping. The danger is that we shall not use to their full capacities all of these allergists, whatever their age and whatever their skill for the further development of American Medicine. There is a place for the strength of youth and the wisdom of age. There is no place for anyone or anything which insists on labeling each of us and filing each fact in the proper drawer. The only danger that faces allergy in this country is regimentation and hardening of the arteries in its leaders. The fact that we appear to some to be over-organized is our salvation in this time of need. What we need is living room and the opportunity to make mistakes.

—JONATHAN FORMAN

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## RESEARCH FELLOWSHIPS AVAILABLE IN CONSIDERATION OF STANDARDIZATION OF ALLERGENIC EXTRACTS

The Board of Regents of the American College of Allergists has just made available one fellowship paying up to \$1,500 a year, to continue for two years. This fellowship is at the disposal of the Standardization Committee and will be used to augment research directed at gaining fundamental knowledge necessary for the development of satisfactory methods for the standardization of allergenic extracts.

The Standardization Committee would appreciate hearing from anyone who is, himself, interested in this work, or who knows of anyone else so interested. It is important that a competent Fellow be selected and be placed in a laboratory where facilities, both intellectual and physical, are most conducive for carrying on successful research. Anyone interested or having information bearing on this matter should communicate with Dr. George E. Rockwell, 2500 Melrose Avenue, Cincinnati 6, Ohio.

Let us all consider the great importance of this subject and make every effort to have competent individuals apply for this fellowship. In addi-

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<sup>†</sup>See page 26, issue of January-February, 1944.

## EDITORIAL

tion to the members and Fellows of the College, we invite other men interested in allergy or its allied branches of medicine to co-operate with us in this endeavor, as we all appreciate the great need for a satisfactory method of standardization of extracts. The opportunity offered in such a fellowship is unlimited and should hold a bright future in allergy for further research work.

Since the funds for such research are limited and there is a great need for two such fellowships, it is hoped that members or friends of the College, who are in a position to do so, will aid in this most urgent and valuable function of the organization when advancing our progress in allergy.

J. WARRICK THOMAS, M.D.

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### Allergic Occupational Dermatitis in Our War Industries

*(Continued from Page 395)*

Hardening or the development of a state of hyposensitivity by continued exposure to the sensitizing chemical has been repeatedly observed in industry. It was because of such observations on Dr. Schwartz's part that the workers in the munitions industries were allowed to continue with their work, in spite of the fact they had developed a dermatitis. The mechanism of the production of this relatively lessened sensitive state needs further study. It does not take place with equal facility with all chemical sensitizers; while it usually occurs in those moderately sensitive, it may fail to appear in those apparently very little sensitive, and may be of very striking and unexpected phenomenon in some extremely sensitive individuals. It is acquired by continuous exposure which has to be guided and it is lost by most individuals when exposure is discontinued.

Hardening is not ordinarily seen in civilian life because the exposure is not continuous or great enough in most instances and when sensitivity occurs only the more sensitive usually consult the physician. It is the worker with marked sensitivity who is among the group who do not become hardened.

If a practical plan for inducing a state of hyposensitivity in allergic contact dermatitis could be worked out, it would be of great help not only in industry but in all walks of life where such allergic contact dermatitis is encountered.

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### Experimental Approach to Oral Treatment of Food Allergy

*(Continued from Page 432)*

nativa, contienen un tipo específico de proteosas y peptonas que tienen la capacidad de dar una completa protección contra el choque anafilático a animales intensamente sensibilizados.

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# Progress in Allergy

Under the direction of ETHAN ALLAN BROWN

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## PEDIATRIC ALLERGY

### A Critical Review of Recent Literature

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#### DISORDERS ASSOCIATED WITH OR COMPLICATING ALLERGY

A GENERAL REVIEW of the subject of the exudative diathesis has been published by Czerny<sup>12</sup>, one of the foremost proponents of this conception. He states that newborn infants who require a long time to make up their initial loss of weight, despite sufficient intake of protein, usually develop signs of the exudative diathesis. The earliest signs are intertrigo, the "milk crust" on the scalp and face, and the condition most commonly termed seborrhoeic dermatitis, though true seborrhoea does not appear until puberty. The lesions appear to be due to an increased pressure of the tissue fluids. Intertrigo, which appears in body folds, is primarily due to this and not to lack of cleanliness, although cleanliness is an important factor in treatment. Erythroderma desquamativa is not a part of the exudative diathesis. The clinical manifestations of this diathesis diminish with dehydration, and limitation of fluids to minimal requirements is a basic principle of treatment, as is also the early interruption of exclusive milk feeding. The fat in the milk is not necessarily a factor. Concomitant with the exudative diathesis may appear lingua geographica, strophulus,\* and hypersensitive mucous membranes of the upper respiratory passages. In this country, the consensus, with which I am in complete agreement, is that the more modern concept of the allergic state has replaced the older theory of the exudative diathesis and certainly offers a more hopeful approach for the study of the basic factors which are responsible for the clinical manifestations.

McGee<sup>36</sup> has reported on the significance of fetal hiccoughs and states that these were first described by Ahlfeld in 1903. McGee has collected a series of twenty-one cases of definite hiccough-like spasms in the unborn fetus. The onset varied from four and one-half months of pregnancy to about one month prior to delivery. The hiccough-like spasms recurred about every five seconds, lasted a few minutes and could be palpated as well as heard with a stethoscope. There was a history of allergy in seventeen of the mothers; in ten cases the allergy was gastro-intestinal. Most of the infants after delivery developed allergic symptoms early; ten were clinically sensitive to cow milk. In about 25 per cent of the cases it was possible to produce hiccoughs in the fetus by feeding the mother a particular food. When fetal hiccoughs are observed, the obstetrician should inform the pediatrician so that all precautions will be taken to discover and treat allergic manifestations as soon as possible.

Salmi<sup>43</sup> has published a general report on seventy-two cases in follow-up studies of pylorospasm in infancy, observed in the University Children's Hospital of Hel-

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\*Strophulus is a rather inexact term to denote what we term lichen urticatus, a form of urticaria of unknown origin peculiar to infants and children, which disappears spontaneously at puberty. It is apparently much more common in Europe than in this country.

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sinki, Finland. The cases include those of pyloric stenosis and ranged in age from five months to twenty-one years. Sixty infants and children were observed with special reference to cutaneous allergic manifestations, as eczema, urticaria and strophulus, which occurred in about one-third of these cases as compared with an incidence of the same conditions in one-quarter of a series of 100 control cases. This difference, I believe, is not statistically significant.

Mao<sup>35</sup> reviewed the results of cutaneous skin tests for allergy on 535 resident pupils in the Pennsylvania School for the Deaf. Positive reactions were found in 28.5 per cent while only 2 per cent showed definite clinical manifestations. He stated that the figure for deaf children is 27.41 per cent higher than for the largest numerical group of normal children reported. Curiously, the percentage of positive reactions was practically identical, whether the deafness was congenital (biologic) or acquired. He stated that it is not unreasonable to assume that allergy and deafness have some mutual hereditary background.

Straub<sup>50</sup> published a most interesting communication on the subject of the frequency of allergy in orthodontic patients. A series of 144 children, fifty-eight female and forty-six male, under orthodontic treatment, was studied. Forty-one (39.4 per cent) were found who had chronic nasal allergy. This high percentage of allergic patients with the typical picture of nasal blockage and paranasal depressions, pinched nares, contraction of the maxillary arches with protraction of the anterior teeth, receding chins and lack of development in facial growth, suggests that in most cases of nasal blockage, allergy must be suspected and considered definitely related to the development of the dentofacial anomalies. In seven cases (17 per cent) of these children, allergic gingivitis was diagnosed. No relationship was found between allergy and the presence or absence of lactobacilli. The author agrees with those who urge the early diagnosis and treatment of nasal allergic conditions as an important method of reducing the incidence of dentofacial anomalies.

Under the term of "asthmatic pseudo-rickets," Bock<sup>5</sup> has described the deformities of the thorax occurring in children with asthma. The chief differences in appearance from true rickets in these deformities are that in this condition the upper transverse diameter of the thorax is greatly narrowed, while in asthmatic pseudo-rickets, the upper transverse diameter is greatly enlarged. This gives, roughly speaking, in both instances a pear-like appearance to the trunk. In asthmatic pseudo-rickets, the larger portion of the pear corresponds to the upper thorax while in true rickets, the pear appears inverted with the larger portion of the pear corresponding to the commonly distended abdomen below the flaring lower costal margins. In both instances the basic mechanism is the same, i.e., the effect of respiration under abnormal conditions. In rickets the primary factor is the softness of the thoracic cage itself undergoing a response to normal muscle pull; in asthmatic pseudo-rickets the primary factor is the abnormal muscle pull on the thoracic cage.

Hansen-Pruss and Goodman<sup>28</sup> employ the term "allergic pulmonary consolidations" to designate the clinical picture most commonly described under the term of "Loeffler's syndrome" which does not give a clue to the allergic origin of the condition. Six cases are discussed in detail. All cases occurred in adults excepting for one, a boy, one year old. Severe asthma, often of long standing duration, was the outstanding presenting symptom. In general the syndrome of allergic pulmonary consolidation is featured by: (1) varying degrees of pulmonary consolidation, at times multiple, often migratory and recognized by roentgenographic examination of the chest; (2) its occurrence in allergic individuals; (3) a varying leukocytosis and eosinophilia; (4) an afebrile course; (5) persistent severe asthma; (6) lack of response to known sulfonamides, and (7) history of frequent upper respiratory infections.

Field<sup>18</sup> describes the case of an asthmatic girl four years of age who, on admission to the hospital following a severe attack of asthma, had subcutaneous emphysema

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extending around the neck, on the face and over the chest, abdomen and thighs. A roentgenogram showed collapse of the left lower lobe. Ten days later she developed a right sided pneumothorax with massive collapse of the left lung and partial collapse of the right upper lobe. The child made a good recovery.

Hansel<sup>26</sup> observed that chronic sinus allergy in children is not infrequently complicated by infection. The most definite and reliable diagnostic feature in differentiating allergy from infection is the examination of the nasal secretions for eosinophilia, observing the relative proportion of these to the neutrophil cells.

Brown<sup>7</sup> reported a case of eczema vaccinatum in a five-month-old boy who had had eczema since the age of one month and had been exposed to a previously vaccinated sister. Sulfathiazole was used orally and locally. The temperature returned to normal in about seven days while the lesions healed. Brown states that the use of the sulfonamide drugs in treating this condition has been an important factor in lowering the mortality rate though the mechanism by which this may be helpful is not completely understood. They may possibly act by eliminating the secondary infection. She also stresses the importance of avoiding any exposure of an unvaccinated child with eczema to vaccine virus in any way, however indirect.

Wenner<sup>55</sup> states that the most common filterable virus which occasionally complicates eczema is the virus of vaccinia. In 1877 Kaposi described a rare type of eruption occurring as a complication of infantile eczema. He saw 10 cases of this varicella-like eruption which had not been previously described and called it "eczema herpetiforme." Wenner described 3 cases in infants, two girls aged five and eight months, respectively, and a boy aged 20 months. The disease is characterized by an eruption which passes through the stages of papule, vesicle, pustule and crust. The lesions appeared in crops, had a transitional course lasting seven to ten days, and in two of the infants spread by confluence to attack *en masse* large areas of skin. During the first week of the disease new vesicles, which also quickly became purulent, appeared, scattered among the pustules. The mucous membrane of the mouth was the seat of small, reddened ecchymotic lesions up to 2 millimeters in diameter. There was fever and a relative leukopenia. One infant died with symptoms of encephalitis but this condition could not be confirmed by necropsy. The chief differential diagnosis would appear to be from eczema vaccinatum. However, from all three of the author's cases a virus similar to, if not identical with, the virus of herpes simplex was isolated.

## IDIOSYNCRASY

Bass<sup>3</sup> reported three cases of sensitivity to mercury. One occurred in a boy ten years of age who developed a rash from accidental contact with metallic mercury. The second was a girl fourteen years of age with a history of eruptions following the use of calomel at four years; later she developed a rash from blue soap presumed to contain mercury, and at the age of seven years developed a rash from ointment containing yellow oxide of mercury. At the ages of twelve and thirteen years she developed an eruption on her lips and cheeks when some teeth were filled with a mercury amalgam. At the age of fourteen years mercury amalgam fillings were again used, and a week later she developed generalized urticaria. After three weeks without relief from various forms of therapy, the amalgam fillings were removed. This was followed by an acute exacerbation of the symptoms, but within twenty-four hours the symptoms subsided and the child remained completely well. A passive transfer test was positive when the site was rubbed with ammoniated mercury; a control site was completely negative. A third case was a girl known to be sensitive to ammoniated mercury who developed a swelling of the lips with a rash about the mouth and cheeks following an amalgam filling. The filling was not removed and the rash disappeared two

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days later. The literature on the subject of idiosyncrasy to mercury in amalgam fillings is well reviewed.

Gibel and Kramer<sup>21</sup> point out that the value of mercury preparations in children is beyond question and their widespread use for many generations with relatively few reports in the literature of harmful action attests to the relative safety of the preparations. Reactions caused by locally applied mercury preparations are to be considered as true idiosyncrasy and not as poisoning. The authors report a case in a twenty-two-month-old girl who was treated for impetigo with 5 per cent ammoniated mercury ointment. Eleven days after treatment she developed a severe, generalized erythematous morbilliform eruption diagnosed by one physician as measles and by another as scarlet fever. She was hospitalized and the skin returned to normal after twenty-four days. The second case is reported in an infant 14 months of age whose diapers were rinsed in 1:4000 bichloride of mercury solution. After six days' use, he developed a diaper area erythema and induration, fever, and a generalized macular rash resembling measles in the less confluent areas and scarlet fever where the rash was confluent. Later blebs appeared. The skin returned to normal in about fourteen days. The authors point out that it is not unusual for a patient to be susceptible to one compound of mercury and not to another, and that the same patient may get different types of reaction depending upon the compound of the drug used. The interval between the application of the drug and the appearance of the eruption varies between one and twelve days. The treatment is symptomatic. Twelve cases of idiosyncrasy to ammoniated mercury have been reported from 1883 to 1942. No case of death caused by local application of a mercury preparation to the unbroken skin has been reported.

Scott<sup>46</sup> reported two cases in which severe reactions to ephedrine occurred although both cases had been treated previously with ephedrine without ill effects. A twelve-year-old girl, following the use of a 1 per cent ephedrine solution in the nose, developed a severe reaction consisting of chilliness, dryness of the throat, palpitations and restlessness. A boy six years of age who followed his usual practice of taking ephedrine for an asthmatic attack, developed a severe reaction characterized by restlessness, anxiety, thirst, rapid pulse and respirations. Scott could offer no explanation for the occurrence of these reactions. I cannot agree with Hansel's<sup>25</sup> explanation that the doses taken were overdoses and that  $\frac{3}{8}$  grain (25 mg.) is a very large dose for a child. The doses which Hansel recommends,  $\frac{1}{8}$  grain (8 mg.) for a child and  $\frac{1}{4}$  grain (16 mg.) for an adult are entirely inadequate in my practice except in those few instances where experience has shown that small doses are adequate for relief.

### ETIOLOGICAL FACTORS

Simon<sup>47</sup> has reported evidence showing the etiological significance of human dander in the pathogenesis of infantile eczema. The evidence consists of: positive skin reactions to patch tests with human dander in fifteen of twenty infants and young children with eczema, whereas in twenty-three control cases there was only one positive reaction to the patch test; the fact that all children are exposed to human dander, either from their own scalps or from those of parents or others with whom they come into contact, the prompt clinical improvement in three of four cases following the institution of measures directed at the avoidance of contact with human dander and reproduction of the lesions at will in four cases out of four attempts on a previously uninvolved skin area by exposure of this area to contact with human dander.

In another communication Simon<sup>48</sup> describes methods of preparing the dander for scratch, patch and intradermal testing. He suggests that possibly the contact re-

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action to human dander represents the so-called "seborrhoeic element" of infantile eczema and that this element is in reality an allergic, probably atopic, response to surface contact with human dander having its source chiefly in the scalp (and secondarily on the clothing, et cetera) of parents and others, possibly even the child itself. The work reported, if confirmed by other investigators, should be of considerable assistance to the pediatric allergist in clearing up many cases of infantile eczema which have hitherto resisted treatment. It also makes it imperative to consider this factor in controlling the environment of all eczematous infants and offers another explanation of an environmental factor from which the eczematous child is commonly relieved when removed from the home atmosphere to that of a hospital. Possibly much the same could be said for the work of Horesh<sup>29</sup> who pointed out that the importance of the fact that foods may act as inhalants and produce allergic symptoms has not been sufficiently emphasized in the management of infantile eczema. He reported nine cases collected over a period of seven years in infants and children due to food odors. Acute exacerbations occurred in five cases when eggs were opened in the presence of the child; in one case when the child was exposed to the odor of freshly dressed fowl; and four other cases due to the odor of frying fish, pork and bacon, respectively, and one from the odor of cooking cabbage. In all cases the child gave positive skin tests to these allergens by the scratch method from 2 to 4 plus. The author suggests that exposure to odors should be sought as a possible cause of otherwise inexplicable exacerbations, especially where the patient has not responded to the prescribed elimination diet. It is not commonly practical or necessary to keep all the reacting foods out of the house. It is usually sufficient to keep the child out of the kitchen where the food is being prepared. The possibility of sensitizing allergic children by food odors must also be considered. Horesh<sup>30</sup> further reported the case of a boy who had had eczema and who developed asthma at the age of two years. He gave, among other positive tests, a 4 plus reaction to white potato. A severe attack occurred when he went into the kitchen where white potatoes were being peeled. An attack was also produced when canned potatoes were opened in the house. The boy's asthma disappeared on complete removal of white potatoes from his environment.

### PROPHYLAXIS AND TREATMENT—GENERAL CONSIDERATIONS

Cooke<sup>10</sup> states that atopic asthma is the type most frequently encountered in infants and children and young adults and its onset is rare after the age of forty; infectious asthma may occur at any time from infancy to old age. Children up to eighteen years need little attention to the sinuses, if recurring infections can be controlled. The early removal of infected tonsils and adenoids is one of the best means of control. As sedatives in asthma, appropriate doses of codeine or pantopon may be given children when necessary. If these drugs produce vomiting at first, so much the better, for it is more effective than coughing in removing mucous plugs. For the definite purpose of producing vomiting in children, however, syrup of ipecac in doses of one-half to one teaspoon may be given.

Criep<sup>11</sup> has emphasized the facts commonly accepted by allergists, that the treatment of hay fever in children is an effective prophylactic measure against the development of bronchial asthma; that children can tolerate the same dosage of pollen extracts as adults; and that no child is too young to take pollen therapy. Unger and Wolf<sup>53</sup> also emphasize prophylactic measures and early study in bronchial asthma, pointing out the fact that the best results obtained in the treatment of bronchial asthma are in those cases in which the condition is treated during the first decade of life.

Hurst<sup>32</sup>, reviewing the etiology and treatment of bronchial asthma in childhood, concludes that "every asthmatic can derive much benefit from good advice. He can be taught a way of life; how to avoid the exciting causes of his particular brand

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of asthma; how to control attacks he is unable to prevent; and, above all, how to be happy in spite of the bad luck of having been born with the asthma diathesis." Rogerson<sup>42</sup> states that the asthmatic child has a special personality type with above the average intelligence. He is apt to be irritable, aggressive, quick to respond, over-anxious, insecure and lacks self-confidence.

Schwartzman, Dragutsky and Rock<sup>45</sup> studied a series of 128 absolutely healthy children (boarders) who were admitted to the hospital for reasons totally unrelated to their health. One hundred and eleven were younger than two years of age. In the group younger than two years of age superimposed illness (morbidity) occurred in 6.36 per cent of cases, chiefly upper respiratory infections. There was no mortality, and in the group older than two years of age, there was no morbidity. The morbidity of 6.36 per cent in boarders younger than two years of age is compared with a morbidity of 66.6 per cent in infants admitted to the same hospital because of uncomplicated infantile eczema. This is very close to the morbidity reported from Milwaukee (58.9 per cent) but almost twice the morbidity reported from Rochester, New York (31 per cent). The contrast in the morbidity and mortality figures between true boarders and eczema in the hospital was marked. This fact seems to show that although the true boarder was exposed to dangers and was susceptible, he was not as vulnerable to infection as was the child with eczema, whose resistance was apparently impaired. This confirms the impression that the condition of the skin plays an important role in resistance to infections. It is concluded that healthy children should not needlessly be admitted to a hospital and particularly that children with eczema or with any other skin condition which can be treated at home should not be hospitalized.

### GASTRO-INTESTINAL AND FOOD ALLERGY

Fries and Mogil<sup>20</sup> studied thirty children following the ingestion of barium meals containing foods to which they were sensitive. The most frequent gastric findings were hypotonicity with delayed emptying. Alterations in the small intestine pattern were infrequent and when present consisted of increased segmentation or, in rare cases, of accelerated motility. Hypertonicity of the transverse and descending colon was an infrequent finding. Rectal instillations of allergen-barium mixtures produced constriction of the colon, or occasionally dilatation. Proprietary barium mixtures containing small amounts of flavoring food stuffs produced changes in the roentgenograms of children sensitive to those foods.

McKhann, Spector and Meserve<sup>38</sup> report that evidence of gastro-intestinal allergy was found in four cases of celiac disease, two of which showed positive skin tests to banana. Elimination of the suspected foods resulted in definite improvement and in an increase in absorption of fats and glucose from the gastro-intestinal tract. Two cases of gastro-intestinal allergy in which the symptoms were suggestive of celiac disease, both of whom gave many positive skin reactions, were improved by elimination of the suspected foods. *They conclude that it is likely that gastro-intestinal allergy bears a causal relationship to the celiac syndrome.*

McLendon and Jaeger<sup>39</sup> listed the symptoms in the syndrome of milk intolerance as follows, in the order of the frequency with which they occur: constipation, anorexia, abdominal discomfort, pallor, a fatigue complex with lassitude and poor posture, disturbed sleep, recurrent diarrhea, respiratory disturbances and urinary disturbances. The characteristic features of the history obtained in such cases are: a family history of allergy, excessive milk ingestion during the latter months of gestation, early ingestion by the infant of cow's milk, the colic syndrome, frequent formula changes with transient relief following such changes, the usual treatments for constipation in infancy, and less acute symptoms as time goes on and solid foods are added, and development of the symptoms listed above as the child develops. Curiously eczema was not of common occurrences in this series. Geographic tongues



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were found in about 10 per cent of the cases and in some instances could be produced at will by giving a particular food. Treatment of the entity described was by the elimination of milk which resulted, in most cases, in dramatic improvement.

In the treatment of allergy to cow milk, the best substitute for human breast milk has been soy bean milk. None of the other substitutes as those made from nuts, poppyseed, taro flour, hydrolized casein, and various other foods, principally carbohydrates, has been completely adequate. This is unfortunate since with the ever-increasing use of soy bean as an article of diet and in industry sensitivity to this substance may be expected to increase. At the suggestion of Dr. Albert H. Rowe of California, the Clapp Company of Rochester, New York, prepared a number of very finely strained meats. Glaser<sup>23,24</sup>, describes their use as the protein basis for milk substitutes in formulas which permit great flexibility with complete satisfaction of protein requirements. These preparations will not be commercially available until after the war. In his report the method of use of such meat-milk substitutes is described and case reports given. It is suggested that theoretically the perfect meat base for an artificial milk for human infant would be human muscle tissue.

In Ratner's discussion of Glaser's paper<sup>24</sup> he states that he has found evaporated milk very effective in the treatment of the milk sensitive child; that when evaporated milk fails to relieve the milk sensitive eczematous child other factors must be sought, especially environmental factors; that the treatment of secondary infections must be carried out and that existing constitutional factors, as hypothyroidism, must be corrected. In my experience cow milk sensitive infants who can tolerate evaporated milk or any other form of cow milk are very uncommon. It is my feeling that most of the reluctance to the use of cow milk substitutes arises because of the impression that cow milk is a "natural" food for human infants. I should like to point out that cow milk is not a natural food for human infants but is designed primarily for calves. The only natural food for the human infant is human breast milk, at least during the first few months of life. That perfectly normal children may be raised from birth without ever having taken any animal milk of any kind has been demonstrated repeatedly. Other factors than food often cause eczema but I particularly dislike to see practically every failure in the treatment of allergic children attributed to lack of proper "environmental control." Environmental control is important and new factors are constantly being discovered, as evidenced by the brilliant work of Simon<sup>47,48</sup>, mentioned above, but the fact is that allergists are getting accustomed to hide their failures behind this term in much the same way that internists attribute so many of their failures to the "neurotic constitution" of the patient. While it is true that secondary infections may retard recovery from eczema, the treatment of such infections seldom presents any formidable obstacles. As regards hypothyroidism, I have never administered thyroid to infants because of eczema alone as I am not satisfied that eczema, unlike urticaria or rhinitis clinically resembling allergic rhinitis, can ever occur as a solitary clinical manifestation of hypothyroidism. In older children with eczema I have uniformly found somewhat reduced metabolic rates but have rarely seen improvement of the eczema as a result of feeding thyroid.

## VITAMINS AND METABOLISM

The above discussed report on celiac disease<sup>38</sup>, a condition accompanied by poor absorption of vitamin A, is of particular interest in connection with the report of diSant Agnese and Larkin<sup>44</sup>, who found that the vitamin A absorption capacity was impaired in four cases of intractable infantile eczema. Each of these cases was characterized by retarded development, malnutrition, severe generalized eczema, marked lymphadenopathy, high blood eosinophilia, frequent respiratory infections, and refractiveness to lack and dietetic treatment. Vitamin A blood levels were determined before and after the ingestion of oleum percomorphum.

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The authors suggest that the respiratory infections and malnutrition observed in infantile eczema may be due to vitamin A deficiency resulting from a defect in intestinal absorption.

Harris and Gay<sup>27</sup> used the whole vitamin B complex in the treatment of infantile eczema. Of twenty unselected infants, an immediate improvement manifested by a decrease in pruritis and a tendency toward healing was noted in eighteen. However, in the final analysis, only two healed completely, eleven improved, and seven showed no change. Although many patients were known to be sensitive to certain articles of diet, no change in diet was made during this study.

Surányi<sup>51</sup> reported good results using nicotinic acid and nicotinic acid amide in children in the treatment of urticaria, asthma, spastic bronchitis and less clearly in eczema. He gave 0.025 gm. to 0.05 gm. orally twice a day before meals. He stated that the drug seemed to be absolutely harmless. However, it would seem to me that 50 mg. of nicotinic acid would almost certainly cause symptoms in an infant while the amide might not.

Zahorsky<sup>57</sup> states that because of the fact that breast fed infants so rarely develop scurvy and that sensitivity to orange juice is rather easily acquired, the feeding of orange juice to breast-fed infants under four months of age is contraindicated. However, since it is known that the vitamin C content of breast milk is dependent upon the mother's diet, in accordance with many pediatricians I feel it advisable to give the breast-fed infant added vitamin C starting at the age of three or four weeks. Glaser and Landau,<sup>22</sup> in 1936, advised the use of ascorbic acid instead of fruit juice in the prophylaxis of allergic disease. Since Bowen<sup>5</sup> has called attention to the use of excipients in the commonly supplied ascorbic acid tablets which are subject to variation and which in themselves may sensitize, I have been using, in order to avoid this, capsules of crystalline ascorbic acid, with instructions to use the contents of a capsule, usually prescribing 50 mg. a day. The capsules are but very little more expensive than the tablets. Cane sugar or some other commonly non-allergic substance may be used as an excipient in the preparation of the capsules.

Howe<sup>31</sup> states that some years ago Dr. R. A. Hetler called his attention to a syndrome frequently associated with nasal allergy in children and which she termed "hyponuclemia." The condition occurs most frequently in children under fourteen years of age and is due to a lack of nucleoprotein in their diet, or to some faulty digestion of nucleoproteins or to a nucleoprotein leak in some purulent discharge in the respiratory tract. To the symptoms Dr. Hetler mentioned—distinct pallor, excess weight, appearance of pseudo-robustness, Howe added anorexia, sluggish mental and physical responses, indifference to play and surroundings, soft and unhealthy flesh, and a somewhat retarded growth. He states that patients with frequent recurrent colds will sooner or later develop hyponuclemia. Good results are reported on treating with nucleic acid, under ten years giving 10 grains or 0.65 gm.; over ten years 15 grains or 1.0 gm. in powder mixed with water, milk or orange juice, twice a day a half hour before meals. He also gives diet rich in natural sources of nucleic acid as, lean meats, all glandular tissues, whole cereals and green vegetables.

Donovan and Harsh<sup>15</sup> experimented with controlled sodium and potassium diets in asthmatic and non-allergic children. They discovered that asthmatic children ingested slightly more sodium than did the non-allergic children on both the high sodium and high potassium diets. The plasma potassium concentration of the asthmatic children on the high sodium diet was slightly higher than it was on the high potassium diet, and slightly higher than the plasma concentration of the non-allergic children on either diet. The plasma sodium concentration of the asthmatic children on the high sodium diet was slightly lower than that of the non-allergic children despite a slightly greater intake. The asthmatic children excreted more

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sodium and more acid in the urine on both diets than did the nonallergic children. The acid base balance of the blood was not studied but the greater secretion of acid by the asthmatic children suggests that they might have shown a relative alkalosis.

### PATHOLOGY

Larkin and his co-workers<sup>34</sup> note that while lymphadenopathy, which may be more or less generalized, involving even the mediastinal nodes, has been commonly noted in patients with eczema, they were unable to discover any reference to the histological appearance of the lymph nodes in infantile eczema. They observed that the degree of enlargement of the nodes is not necessarily related to the severity of the skin lesions but was most marked in those patients who fall into the group described by Hill as "atopic erythroderma." The characteristic histological picture was found to be replacement of the lymphatic tissue with proliferated reticulum cells, histiocytes and fibroblasts. Many of the histiocytes are lipophages and melanin and iron are present. Identical changes have been reported by Hurwitt under the name of "dermatophytic lymphadenitis" in lymph nodes removed from adults with chronic non-specific skin diseases characterized by pruritus. In the more severe cases the degree and generalized nature of the lymphadenopathy, together with the poor nutritional state of the infant and frequent high leukocyte counts suggested clinically a blood dyscrasia, or possibly Hodgkin's disease. The benign nature of the condition, however, is evident as the cases are observed over long periods of time, and the conclusions of those who have studied the condition, including Hurwitt and the authors, are that the adenopathy is of a benign reactive nature in response to the skin disease as an irritant.

Lamson, Butt and Stickler<sup>35</sup> have reported on the clinical and autopsy findings of eighty-two adults and four children with "fatal asthma." No evidence of "general lymphoid hyperplasia" was found in the case of the children. The authors agree with Tuft that "there is at present no known pathological picture, either gross or microscopic, which may be considered characteristic or pathognomonic of asthma."

### SKIN TESTS

Albert and Walzer<sup>1</sup> have described a distinct type of contact reaction which occurs almost exclusively among atopic individuals, particularly children, and is elicited by application to the skin of oil-free allergens. One or more positive reactions were obtained in 75 per cent of atopic children with asthma, in 75 per cent with vernal catarrh, in 62.5 per cent with eczema and neurodermatitis, and in 60 per cent with hay fever. The high incidence of contact reactions in vernal catarrh is suggestive evidence of the atopic nature of this illness. Silkworm and feathers gave the highest number of positive contact reactions with almost equal frequency among the various atopic illnesses. Reactions to pollens tended to occur more frequently among patients with hay fever and vernal catarrh than among those with other allergic conditions. Allergenic foods rarely gave positive contact reactions. The clinical applications of this method of testing was not discussed.

Stoesser<sup>19</sup> discussing skin testing, states that he prefers the puncture technique, using one to three punctures through a droplet of material. His experience confirms the generally accepted impression of the importance of the ingestants in early childhood, with the increasing importance of inhalants as age advances. He found that the reactions to milk, egg, and cheese were most significant in eczema; to meat, fish and nuts in asthma; and to cereals, dairy foods and chocolate in allergic rhinitis. Skin tests in urticaria were generally unsatisfactory, but if positive reactions were obtained to fruit, vegetables or nuts, they were usually of clinical significance. The size of the reaction is not always an index of its clinical importance. Positive

reactions from animal emanations, and cottonseed were generally of value, regardless of the size of the reaction. An interesting finding was that in occasional instances localized areas were found where non-specific reactions occurred due to hyperirritability of the skin. Increased sensitivity to touch was found in these areas which had to be avoided in the interests of accurate testing. Farmer<sup>17</sup> reported the analysis of results of cutaneous scratch tests on fifty patients with eczema in Australia. Horse dander was the most common offender in the inhalant group reacting in about half the cases. Next in frequency were house dust and feathers. Egg white was the commonest reactor in the food group, followed by wheat and milk. Wingard<sup>56</sup> studied the cutaneous reactions of nine patients to their own blood serum at varying intervals after ingestion of known offending foods. Delayed reactions were observed in six of the nine patients, indicating that the offending allergen was present in the blood. No reactions were observed in twenty non-allergic controls. It was concluded that the delayed reactions which followed the intracutaneous injection of autoserum in food sensitive individuals were due to the same substance which causes the clinical symptoms. Ditkowsky<sup>14</sup> and associates report that sensitization to egg white, if it occurs via the placenta, would probably depend in a great part on a non-coagulable fraction (ovomucoid), since coagulated egg white would lose its characteristics during the process of digestion and would not reach the placenta in a form capable of stimulating immunological processes. The uncoagulable fraction could, however, reach the placenta and be passed over to the infant. The correctness of this theory might be proven by cutaneous tests on atopic children with the different fractions of egg white. Forty-six infants, half of whom were under one year of age, with typical atopic dermatitis were tested with egg white fractions and, incidentally, to chicken feathers. There were forty-one positive reactions to ovomucoid, forty to dried egg white, twenty-two to ovalbumin, seventeen to chicken feathers, fifteen to conalbumin, and 9 to ovomucin. These experiments would tend to bear out the thesis (since both dried and fresh egg white contain ovomucoid) that since ovomucoid is the most resistant of the egg-white fractions one might expect it to be responsible for and it is in fact the cause of the greatest number of positive reactions to cutaneous tests with egg white in infants and young children with atopic dermatitis. These observations also confirm the clinical fact that sensitization to egg white does not necessarily carry with it sensitization to chicken feathers or serum (conalbumin). It is also interesting in the above series that only six patients giving positive reactions to egg white were clinically sensitive to egg white. The others could be exposed to it without apparent harm.

## DRUG THERAPY

Although the use of derivatives of opium is rather generally condemned by most allergists, nevertheless many, myself included, feel that these preparations do have a very distinct place in the treatment of bronchial asthma if given in properly selected cases and in small doses. In this connection, the introduction of the new drug, demerol, may be of considerable value because it appears to have most of the advantages of the alkaloids of opium without many of the disadvantages. This drug was discussed by Batterman and Himmelsbach<sup>1</sup> who state that the preparation, a synthetic product, is closely related, structurally, to atropin and somewhat to morphine. Like the commonly employed narcotics it may be habit-forming. It possesses three chief reactions: analgesia, spasmolysis, and sedation. Unlike morphine, it does not endanger life and does not lessen expectoration. An acute attack of asthma in an adult can be relieved by the subcutaneous injection of 35 mg. Good results have been obtained using this amount with half the amount of epinephrine usually given the asthmatic individual. Thus far I have noted no reports of its use in children.

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Despite practically universal failure to find a use for histaminase in the treatment of allergic conditions, its effect continues to be investigated. Peshkin<sup>40</sup> and his co-workers stated that in forty-eight children with various allergic diseases who were given daily doses of 50 units of histaminase, no beneficial results were observed. Toomey and his associates<sup>52</sup> reported that histaminase neither prevents nor ameliorates the serum sickness which follows the administration of meningococcus antitoxin (horse). However, the search for the philosopher's stone of allergic therapy continues. Wasson<sup>54</sup> employed ethylene disulfonate in the treatment of allergic children. The basis for the use of this preparation is a report by Bodman and Maisin in 1940 to the effect that an abnormality of carbohydrate metabolism is the primary cause of the allergic state and is due to the absence of certain catalysts of coenzymal activity in the body. They found that ethylene disulfonate fulfilled the requirements of such a catalyst *in vitro* and discussed the effects of the intramuscular injection of this drug. Wasson treated twenty allergic children using twenty others as controls under approximately standard conditions. He concluded that the treated group may have benefited sufficiently so that the drug deserves further study. Bartlett<sup>2</sup> treated 247 children with ethylene disulphonate. The patients ranged in age from four months to sixteen years and showed various allergic manifestations. There were no control cases and the author states that skin testing was not thoroughly carried out because he felt that this was unnecessary as well as unsatisfactory. While under therapy foods known to disagree clinically with the patient were omitted; the sugar in the diet was reduced and the fat usually increased. The following drugs, which are said to be contraindicated during ethylene disulphonate therapy were also omitted: barbiturates, opiates, anesthetics, alcohol, sulfa drugs and quinine and its derivatives. The dosage of the drug was 2.00 c.c. intramuscularly and a second dose was rarely given before nine weeks. The average number of doses per patient was 1.41. Satisfactory results are said to have been obtained in over 86 per cent of cases. On the animal experimental side, however, ethylene disulphonate has not done so well. Fisk, Small and Foord<sup>19</sup> experimented with this preparation in guinea pigs sensitized by the administration of egg albumin. They concluded that statistical analysis of the mortality rate revealed that the differences were within the limits of standard error, and state that ethylene disulfonate does not protect guinea pigs against anaphylactic shock.

Dees<sup>13</sup> treated forty-nine adults and six children with suppositories containing 0.25 gms. ( $3\frac{3}{4}$  grains) of aminophyllin. Good relief was usually obtained within twenty minutes and one suppository morning and evening was usually sufficient to keep the patient symptom-free although in severe cases suppositories were used every four hours. The great advantages of this form of medication are that it takes effect rapidly, acts over a long period of time and can be administered by the patient. In using the suppositories recommended by Dees, I have found it occasionally useful to add a sedative, as seconal, to the suppository. One should not use cocoa butter suppositories in patients sensitive to chocolate.

Fabricant and Van Alyea<sup>16</sup> reported on the use of privityne hydrochloride, a new imidazoline derivative, which is crystalline and readily soluble in water or normal saline. In animal experiments they found that a 0.1 per cent solution had no detrimental effect upon ciliary activity. In normal subjects it caused no alteration of the pH of the secretions. There was no irritation of the mucous membrane or any toxic side effects as are sometimes noted with ephedrine. This preparation is available in two strengths, 0.1 per cent and 0.05 per cent. The weaker preparation is recommended for use in children and adults with particularly sensitive nasal mucosæ. It has become known† that in some children privityne is capable of producing a definite sedative effect, which is now being investigated for possible therapeutic use in overly anxious or active children who are to undergo simple, painless

†Personal communication from the Medical Department of Ciba Products, Inc., Summit, N. J.

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procedures such as x-ray investigation requiring light sedation. This sedative effect has been seen only with the 0.1 per cent solution. It is my feeling that if a sedative effect of privity is discovered and does prove harmless that this would increase the benefits of its use for infants and young children, especially during the night when its decongestive effect in the conditions for which it is commonly used, together with sedation, would help secure satisfactory rest.

### MISCELLANEOUS

McIvor and Cherney<sup>37</sup> reported the clinical trial of a new flea antigen which appears to be effective in desensitizing some individuals sensitive to flea bites. Among the cases reported was that of a three-year-old girl who suffered from asthmatic attacks with urticaria. The mother believed these manifestations to be due to flea bites. During the clinical trial of the flea antigen, the child received a series of injections, each resulting in an asthmatic episode. She is said to have been greatly benefited by the treatments.

Conner and Milzer<sup>9</sup> observed that attacks of urticaria occasionally occurred in patients convalescing from scarlet fever. When there was no apparent cause, such as scarletinal antitoxin or possibly human convalescent scarlet fever serum administration, food allergy was commonly considered the cause of the urticaria. The severity of one case of urticaria prompted further study as to whether or not bacterial allergy might be a factor. Three patients who developed urticaria while convalescing from uncomplicated scarlet fever were tested with various preparations from the hemolytic streptococci isolated from their own throats. Positive skin reactions were constantly observed from the intradermal inoculations of suspension of killed washed broth cultures, while the control tests with other substances gave no reactions. The possibility of delayed or hemorrhagic nephritis and non-suppurative arthritis as a manifestation of bacterial allergy was also considered.

Regan<sup>4</sup> reports a type of immediate reaction on primary smallpox vaccination which follows the insertion of the virus at the vaccination site which occurs only in those cases in which the vaccination will subsequently prove successful. This consists in the almost immediate appearance within three to ten minutes of a minute blanched zone which quickly develops into a minute white papule with a faint surrounding erythema. The white papule, resembling an urticarial papule, appears at one part of the scratch line and is so small as to be at the border of ordinary visibility. It may be made clearly visible by the use of a small hand lens which gives a magnification of three diameters. This immediate local reaction of the white papule remains clearly visible under the hand lens magnification for twenty minutes or so; then quickly fades. Regan has apparently discovered the same sign independently which Cohen<sup>8</sup> previously described, although Cohen used the pressure-puncture method instead of the scratch method of making the vaccination.

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# News Items

There will be an informal meeting of all the members of the American College of Allergists, at 8 p. m., Sunday, December 10, at the Waldorf-Astoria, in Assembly Room 4-N-P.

First Lieutenant Samuel S. Burden (MC), F.A.C.A., has received orders to take charge of the Allergy Service at the A.S.F. Regional Hospital, Camp Crowder, Missouri.

F. W. Wittich, M.D., F.A.C.A., of Minneapolis, has been elected an Honorary Member of The Sociedad Argentina de Alergia.

Dr. C. R. K. Johnson, F.A.C.A., will be in charge of the Allergy Department of the Cleveland Clinic, succeeding Dr. J. Warrick Thomas, F.A.C.A., who has now become associated with the Vaughan Memorial Clinic, Richmond, Virginia.

Colonel Frank G. Crandall (MC) USA, Medical Director, Hammond General Hospital, Modesto, California, has recently been elected to Honorary Fellowship in the College for his meritorious research in and contributions to allergy.

Dr. G. Estrada de la Riva, Vedado, Havana, Cuba, has been elected to the Editorial Board of *ANNALS OF ALLERGY*. Dr. Estrada de la Riva will abstract all the scientific articles which appear in the *ANNALS* and will translate these abstracts into Spanish. The Spanish abstracts will take the place of the Spanish summaries which have formerly appeared following each article in the *ANNALS*. Dr. Estrada de la Riva is a graduate of the University of Havana and is Associate Professor of Experimental Bacteriology at that University. Dr. Henry I. Shamon, Captain (MC), Boston, will continue to review the Spanish literature for the *ANNALS*.

## INSTRUCTIONAL COURSES AVAILABLE

Sets of the complete instructional courses presented at the First Annual Meeting of the American College of Allergists in Chicago, Illinois, June 10 and 11, 1944, are available at the nominal charge of 75 cents a set.

Subjects and authors are listed below:

The Eczematoid Dermatoses of Infants and Children—JEROME GLASER, M.D., F.A.C.A. Rochester, N. Y.; CHARLES S. MILLER, M.D., Corona, N. Y.

The Diagnosis and Treatment of Allergy of the Nose and Paranasal Sinuses—FRENCH K. HANSEL, M.D., F.A.C.A., St. Louis, Mo.

Gastro-Intestinal Allergy—ORVAL R. WITHERS, M.D., F.A.C.A., Kansas City, Mo.

Allergy of the Central Nervous System—T. WOOD CLARKE, M.D., F.A.C.A., Utica, N. Y.

Allergic Migraine—J. WARRICK THOMAS, M.D., F.A.C.A., Cleveland, Ohio.

Dermatologic Problems in Allergy—LOUIS A. BRUNSTING, M.D., F.A.C.A., Rochester, Minn.

Bronchial Asthma—LEON UNGER, M.D., F.A.C.A., Chicago, Illinois.

Drug Allergy—ETHAN ALLAN BROWN, M.R.C.S. (London), L.R.C.P. (England), F.A.C.A., Boston, Mass.

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# BOOK REVIEWS

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**ALLERGY IN PRACTICE.** By Samuel M. Feinberg, M.D., Associate Professor of Medicine and Chief of the Division of Allergy, Northwestern University Medical School, Chicago. With the collaboration of Oren C. Durham, Chief Botanist, Abbott Laboratories. Cloth. Price, \$8. 798 pages, with 36 illustrations. Chicago: Year Book Publishers, Inc., 1944.

The author, in his preface, criticizes the majority of previous books on allergy as being "sketchy manuals" or "encyclopedic tomes," and writes a 798-page book, with sixty-seven pages devoted to allergy to common air molds and ninety-eight pages to pollens. More illustrations and graphic line drawings demonstrating techniques, mechanism, the pathology of allergy, et cetera, could have shortened the text, with greater appeal to the student and practitioner.

With the rapid development of our knowledge of allergic diseases, it is difficult to distinguish the important subject matter. This has been made easier by the author, however, by using regular text type for essential, general, accepted material and small type for controversial subjects. There are twenty-six chapters, all summarized, and asthma and hay fever are exhaustively discussed. Differential and etiological diagnosis of all types of allergic manifestations, specific and non-specific therapy, detailed methods for symptomatic relief, elimination measures and techniques are all adequately covered. About one-fifth of the book is devoted to other allergies—"hyperesthetic rhinitis, urticaria and angioneurotic edema, atopic dermatitis and dermatophytosis, contact eczema, allergy of the digestive tract, migraine and allergic headaches, allergy of the eye, and so on." No mention is made of transient pulmonary consolidations with high blood eosinophilia (Loeffler's syndrome), which is considered by many allergists as an expression of allergy. Although convincing evidence has been offered that the Ustilaginales in grain mill dust is a very important factor (nearly one-fourth) to all farmers making their own cattle feed, workers in thousands of dirty "feed" mills (grain) and flour mills and grain storage bins throughout the grain belts of the Middlewest and the Pacific Northwest and Canada, as well as to all of the inhabitants of these cities and towns in these areas, it is surprising that the author would make the statement, when speaking of smuts—"that instances of allergy from such environmental or occupational exposures constitute only a very small portion of the numerous cases of mold allergy due to the spores in the general atmospheric environment."

With the exception of a few unimportant oversights, such as the use of the term "adrenalin" for "epinephrine," the subject is scholarly and is presented in a practical manner which makes the book invaluable to both the student and the specialist. It is recommended to all interested in allergy.

—F. W. W.

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**PATHOLOGICAL STUDY OF THE ACTION OF DENICOTINIZED TOBACCO ON THE ALBINO RAT'S BLOOD VESSELS** (Estudo Patológico da Ação do Tabaco Desnicotinizado sobre os Vasos Sanguíneos do Rato Branco). By Lopes de Faria, University of Minas Geras. Belo Horizonte, Brazil, S. A.: Grafica Queiroz Breiner, Ltd., 1943.

The author discusses tobacco and some of its constituents, but mentions that the principal one is nicotine, principally in combination with malic acid. Later he cites the effects of smoking on the circulatory system. Under this heading he discusses the vasoconstriction of the peripheral capillaries, the angina pectoris syndrome, coronary sclerosis, and thrombo-angiitis obliterans. He refers to the work of Harkavy and Sulzberger, and also of Westcott and Wright. He mentions the fact that some authors claim that the reactions obtained with tobacco extract are specific and others non-specific, i. e., simply an irritating reaction. He also brings out the fact that Friedlander, Silbert and Laskey obtained gangrene of the fingers on the Albino

## BOOK REVIEWS

rats, following an injection with an extract of tobacco, of which 60 per cent of the nicotine had been previously removed. Harkavy repeated the same experiments and found the same results but concluded that these Albino rats were specifically sensitive to the tobacco itself, even though the nicotine was removed before. He ends the first chapter with the anatomical pathology of thrombo-angiitis obliterans.

In the second chapter the author discusses the experiments he performed. Under this heading he goes into detail about the necessary armamentarium needed for these experiments. First, he mentions the materials needed, then the method used. In the experiments of Harkavy he states that the Albino mice received test injections daily, intraperitoneally, of 0.1 cubic centimeter; time of the experiment was six to twelve weeks. During this time gangrene appeared in the fingers of these animals injected with tobacco extract. Only the male animals had gangrene and were sensitized specifically to the tobacco (Proof of Schultz-Dale).

There is an English summary at the end, four pages in length. In the discussion he mentions that there is still need for research as regards the nicotine content of tobacco extracts.

Concerning Harkavy's experiment, the author advances the hypothesis that the varieties of tobacco he employed may have had much lower antigenic power. This lower antigenic power may depend on the varieties of tobacco or on the district in which they were grown (Minas Gerais, Brasil).

He makes the following conclusions:

1. The tobacco grown in Minas, when deprived of its nicotine, produces no specific hypersensitiveness in white rats as shown by the precipitin and the Schultz-Dale tests.

2. The tobacco grown in Minas Gerais, when deprived of its nicotine, does not produce pathological changes in the blood vessels of the heart and of the extremities of white rats.—H. I. S.

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\*"A new type of medication to be used in Bronchial Asthma and other Allergic conditions." New Eng. Jour. of Med., 223:843-846, 1940.

*Literature Upon Request*

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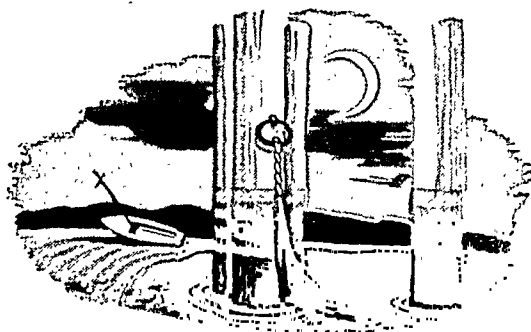
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## *Abstract*

**PALINDROMIC RHEUMATISM:** A "new" oft-recurring disease of joints (arthritis, peri-arthritis, para-arthritis) apparently producing no articular residues—report of thirty-four cases; its relation to "angioneural arthrosis," "allergic rheumatism" and rheumatoid arthritis—P. S. Hench and E. F. Rosenberg, Arch. Int. Med., 73:293, (April) 1944.

Palindromic rheumatism has as outstanding characteristics: multiple afebrile attacks of acute arthritis and peri-arthritis, with pain, swelling, redness and disability of one or more small or large joints in an adult of either sex. Recurrence of the complaints at irregularly spaced intervals has been noted with the attacks being sudden in onset and of comparatively short duration. Six typical cases are described with data on an additional 28 cases being presented in tabulated form. Joints most frequently affected were (in order) the fingers, wrists, shoulders, knees, toes and elbows. All patients stated that the attacks had been very numerous (hundreds of them). No residual pathology could be determined by any means. There were no constitutional reactions during the attacks. Ten of the patients experienced recurring swellings of the para-articular soft tissues. The more common reactions were those of the articular, peri-articular or para-articular tissues, with the presence of nodules in the intra or subcutaneous tissues being somewhat rarer. Total and differential leucocyte counts were normal during and between attacks. Blood uric acid determinations were normal. Sedimentation rates were normal or only slightly elevated.

The authors conclude that some unknown irritant is the causative factor, as no definite gross or microscopic changes could be noted. In the investigation of the etiology, allergic reaction in the joints is considered. Sixteen of the patients had no clinical signs of allergy and eighteen experienced a total of twenty-one varied possibly allergic reactions. Points for and against the allergic factor are mentioned. The attacks could not be correlated with any acute exogenous infection. Rheumatoid arthritis is convincingly differentiated from this condition by the persistent absence of chronic arthritis even after scores of attacks and years of disease. The use of epinephrine and related compounds, histaminase and histamine desensitization has been relatively unsuccessful in the therapy of these 34 patients. Other forms of therapy—fever, measure to combat infection, etc.—are productive of similar results. Patients are more likely to become better than worse with time. No evidence of crippled joints has been reported. L.J.H.



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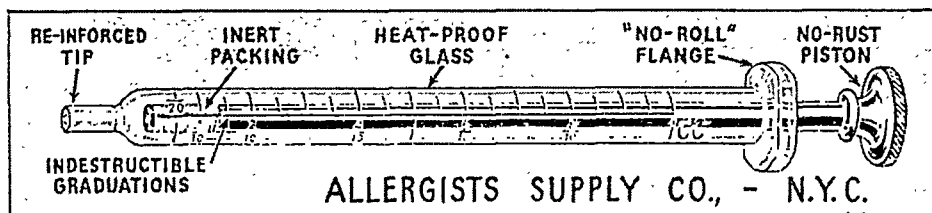
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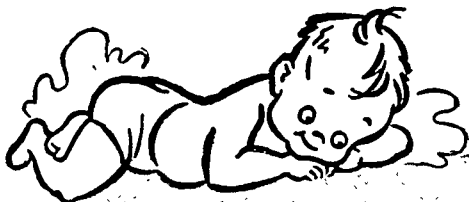
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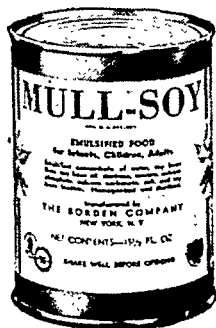
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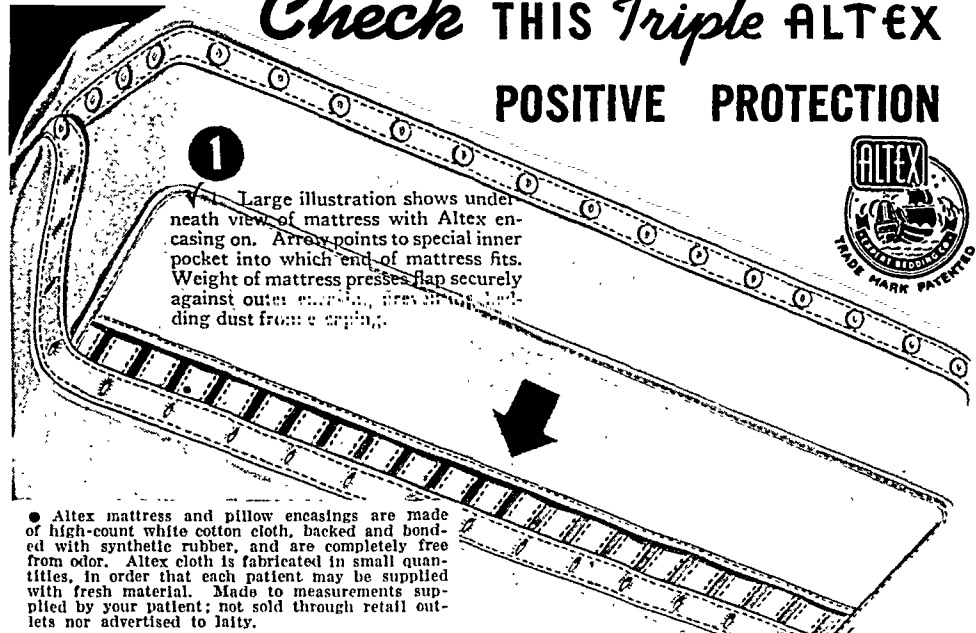
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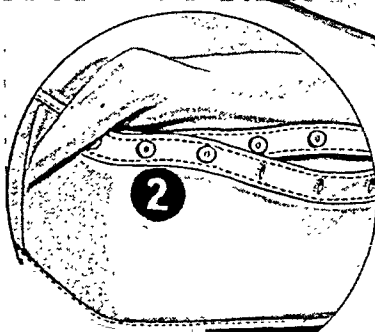


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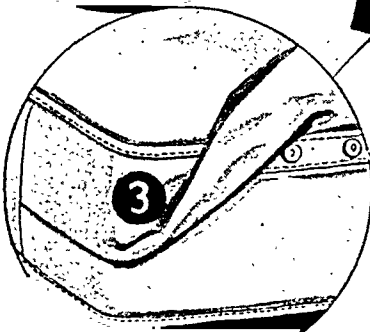
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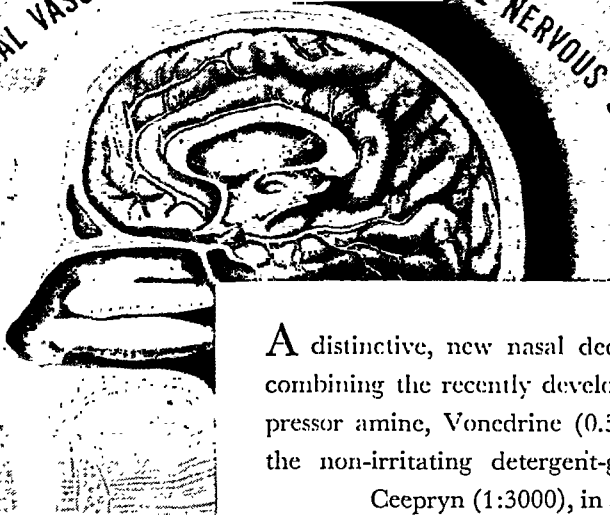
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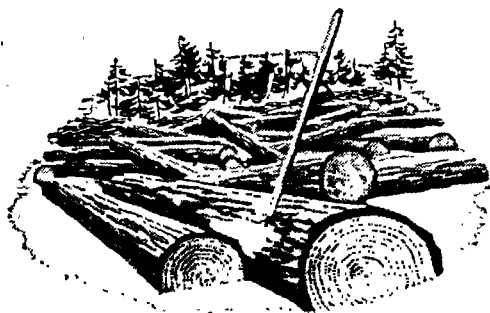
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## THE MECHANISM OF ANAPHYLACTIC AND ALLERGIC REACTIONS

### An Evaluation of the Role of Histamine in Their Production

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Rochester, Minnesota

IT is somewhat difficult to ascribe with justice the first description of an anaphylactic reaction to one individual. The exact origin of the subject is obscured in the early development of immunologic studies. The use of repeated injections of solutions containing foreign protein into animals and man to induce or transfer immunity brought to light the hypersensitive state. The subject is new. It belongs to twentieth-century medicine. Typical of this period, expansion has been rapid. Measured by the doubtful criterion of number of papers published, progress has been quickly made. By 1909, with the subject still in its infancy, Anderson and Rosenau<sup>3</sup> found some 200 papers worthy of citation when they reviewed the literature. Since 1935, Rackemann<sup>44-53</sup> has mentioned more than 100 papers each year in his annual surveys of reports on allergy. Despite this enormous annual accumulation of written material, the mechanism of the hypersensitive state with its associated anaphylactic reaction is still not fully understood.

The early studies of hypersensitivity are linked with three great schools: a group in Germany headed by von Pirquet<sup>43</sup> and Schick, a group in France led by Richet<sup>54</sup> and an American school. Von Pirquet and Schick studied the hypersensitive state in human beings and their observations did much to clarify the subject. The continued use of their tests for tuberculosis and diphtheria is testimony of the accuracy of their research. It was von Pirquet who suggested the term "allergy," which is derived from the Greek words *allos* (change) and *ergon* (reaction), "changed reaction," which is still the most direct definition we have for the hypersensitive state. Richet in France, carried out many of his studies on the dog. Nevertheless, it is difficult to find a description of canine anaphylaxis

among his papers. Many of Richet's publications seem diffuse and at times difficult to follow, with a generous proportion devoted to the development of an elaborate terminology which he used to explain allergic phenomena. Richet introduced the term anaphylaxis, which he derived by compounding the two Greek words *ana* (against) and *phylaxis* (protection), "against protection." He thus defined the hypersensitive state as the opposite to prophylaxis. The extent to which this interpretation may be true is still unsettled.

In America, most of the early studies were made on the guinea pig and were concerned with what may be termed the mechanics of anaphylaxis. Such men as Anderson and Rosenau, Gay and Southard<sup>28</sup> established the procedure to be followed in order to induce the hypersensitive state. They showed that the single or repeated administration of foreign protein is followed some days or weeks later by a hypersensitive period during which reinjection of the protein (shock injection) produces a rather stereotyped response typical for each species of animal and independent of the protein used.

By 1909 the basic framework of anaphylaxis was established and a new chapter in immunologic reactions was in the process of being written. At about this time some investigators turned their interest from strictly immunologic studies to the elucidation of the mechanism by means of which the symptoms of anaphylactic shock are produced. To accomplish this they used physiologic methods of investigation. The animals most thoroughly studied from this point of view have been the guinea pig, the dog and the rabbit.

The formation of a toxic chemical substance during anaphylactic shock was one of the first mechanisms suggested for the production of the symptoms of the reaction (Biedl and Kraus, 1909).<sup>9</sup> That this chemical factor might be histamine was first inferred by Dale and Laidlaw<sup>19</sup> in 1910, when they pointed out the similarity between the phenomena of anaphylactic shock and the physiologic action of histamine. Since the publication of their paper considerable evidence has accumulated in favor of the view that many of the symptoms of anaphylactic shock are due to the liberation of histamine.

#### ANAPHYLAXIS IN THE GUINEA PIG

While Ehrlich, the great German bacteriologist, was visiting America in 1904, Theobald Smith told him that guinea pigs became sick and died when given repeated injections of horse serum. On his return to Germany, Ehrlich gave the problem to Otto (see Anderson and Rosenau, 1909).<sup>3</sup> Otto<sup>42</sup> established the essential features of the reaction and called it the Theobald Smith phenomenon. The term is seldom heard in discussions of anaphylaxis in America today. The predominating symptom of the reaction which Otto described was progressive respiratory difficulty identical with that observed in histamine poisoning in the guinea pig. Gay

and Southard in 1908, pointed out that in fatal reactions respiration ceased in the inspiratory phase and that the lungs were emphysematous. Auer and Lewis<sup>5</sup> in 1910, demonstrated that the respiratory difficulty was caused by contraction of the smooth muscle of the bronchioles. The condition might be termed asthma in the guinea pig. It is exactly duplicated by the injection of histamine into this animal.

Schultz<sup>63</sup> in 1910, in America, and Dale<sup>18</sup> in 1913, in England, demonstrated that isolated perfused uteri from sensitized guinea pigs contracted forcefully upon addition of the sensitizing antigen. The response of the smooth muscle was identical with that given by histamine.

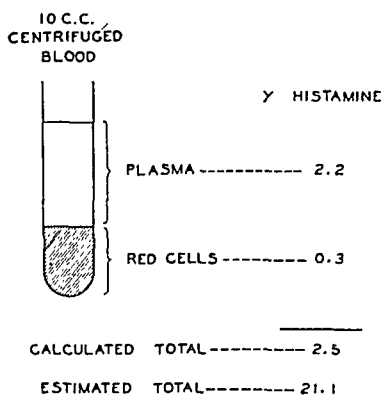
Utilization of the isolated perfused organ technique has recently given more direct evidence of the liberation of histamine during anaphylactic reactions in the tissues of the guinea pig. Bartosch, Feldberg and Nagel<sup>7</sup> in 1932, showed that a histamine-like substance was liberated into the perfusate when the antigen was administered to the isolated perfused lungs of sensitized guinea pigs. Schild, in 1937<sup>61</sup> and 1939<sup>62</sup>, confirmed this observation and extended the study to other organs of the guinea pig. He found that histamine was liberated in readily estimable quantities from the isolated aorta, uterus, liver and lungs of sensitized guinea pigs when these tissues are exposed to the antigen. Schild's experiments also suggest that the contraction of the uterus of sensitized guinea pigs observed by Schultz<sup>63</sup> and Dale<sup>18</sup>, is due to the liberation of histamine following a reaction between the tissue of the uterus and the antigen. He found, rather oddly, that smooth muscle taken from the gastro-intestinal tract of sensitized guinea pigs did not contract on administration of antigen nor did it show liberation of histamine. A further study of this difference between the smooth muscle of the gastro-intestinal tract and the smooth muscle of the aorta and uterus might yield interesting information.

In 1935 Barsoum and Gaddum<sup>6</sup> introduced a quantitative procedure for the estimation of histamine in the blood. Experience with this method led to its modification and the evolution of a somewhat simplified procedure (Code, 1937).<sup>12</sup> The method has given an accurate and highly sensitive tool for the further study of anaphylactic reactions. The advances accomplished by its use have been sufficient to justify their somewhat detailed examination.

The amount of histamine in the blood of animals varies widely in different species. Of the blood of normal animals so far tested, rabbit blood has consistently shown the highest concentration, with values usually ranging from 1 to 2.5 micrograms of histamine base per cubic centimeter of blood. The blood of the guinea pig comes next in line with a histamine content of approximately 0.05 to 0.15 microgram per cubic centimeter. Dogs' blood consistently contains little or no histamine. The blood of man falls between that of the guinea pig and that of the dog with amounts usually ranging from quantities which can just be detected up to about 0.06 microgram per cubic centimeter of blood.

When dealing with a substance possessing such potent physiologic properties as histamine, an important question to answer is: Is the histamine free in the blood to produce its physiologic effects or is it held safely within the cells of the blood? Because of the relatively high con-

#### THE DISTRIBUTION OF HISTAMINE IN UNCLOTTED RABBIT'S BLOOD



#### THE SOURCE OF HISTAMINE IN UNCLOTTED RABBIT'S BLOOD

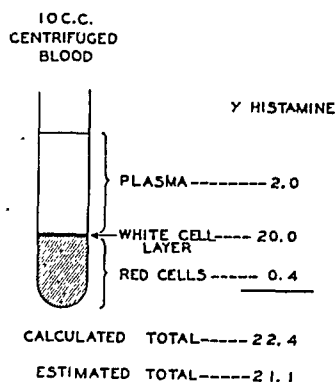


Fig. 1. (left) The distribution of histamine between red cells and plasma in normal rabbits' blood. The amounts of histamine in the plasma and red cells together accounted for only 12 per cent of the total found to be present in 10 c.c. of the whole blood not centrifuged.

Fig. 2 (right) The source of histamine in normal rabbit's blood. When the white cell layer which separates out between plasma and red cells was included in the histamine estimations, it was found to be the major source of the histamine in the blood.

centration of histamine in rabbit's blood, the distribution of the histamine between cells and plasma was first studied in detail in this animal (Code).<sup>13,14</sup> An example of experiments carried out on blood from rabbits will serve to illustrate the consistent findings.

Ten cubic centimeters of heparinized unclotted rabbits' blood was centrifuged. The plasma was found to contain 2.2 micrograms of histamine and the red cells contained even less. Ten cubic centimeters of the same blood not centrifuged contained 21.1 micrograms of histamine. The plasma and red cells together accounted for only 12 per cent of the total amount of histamine present in this sample of blood (Fig. 1). The only portion of the centrifuged blood not studied in this sample was the layer which separates out between the plasma and red cells and contains the leukocytes and platelets—"the white cell layer" or buffy coat. When this layer was included, the missing histamine was recovered. The white cell layer was found to be the major source of the histamine contained in blood. In this example the white cell layer contained 89 per cent of the whole blood histamine (Fig. 2). Using this information, Ing and I in 1937<sup>16</sup>, isolated histamine in pure crystalline form from the white cells of rabbit blood.

The results have been extended to include man, the horse, the bullock, the goat, the calf and the dog. In all these species, 70 to 100 per cent of the blood histamine was found in the white cell layer of centrifuged blood

# MECHANISM OF REACTIONS—CODE

TABLE I. HISTAMINE CONTENT OF THE BLOOD OF GUINEA PIGS BEFORE AND DURING ANAPHYLACTIC SHOCK AND NITROGEN ANOXEMIA

Guinea pig	Conditions	Histamine per c.c. blood, micrograms	
		Before shock	During shock
1	Anaphylactic shock	0.150	0.600
2	Anaphylactic shock	0.127	0.959
3	Anaphylactic shock	0.166	1.250
4	Anaphylactic shock	0.080	0.779
5	Anaphylactic shock	0.184	0.685
6	N <sub>2</sub> anoxemia	0.143	0.118
7	N <sub>2</sub> anoxemia	0.149	0.141
8	N <sub>2</sub> anoxemia	0.118	0.066

(Code, 1937).<sup>13</sup> In general these results have been confirmed by Minard<sup>40</sup> and by Rose<sup>56</sup>, and Rose and Weil.<sup>60</sup> Zon, Ceder and Crigler<sup>60</sup>, and Minard<sup>40</sup>, have found that the platelets of rabbits' blood may contain histamine. It may be concluded that in most species under normal conditions, the white cell elements are the source of the histamine in normal blood.

To return to anaphylactic reactions, the method has been used to determine the changes in the histamine content of the blood of guinea pigs and during anaphylactic shock (Code, 1939).<sup>15</sup> The animals were sensitized to egg white and horse serum. Control samples of blood were withdrawn from the sensitized guinea pigs by cardiac puncture and through the same needle the antigen was immediately injected. When respiratory difficulty was maximal, anaphylactic blood was taken by transection of the vessels of the neck. The results are illustrated in Table I. The first five animals of this series were in a state of anaphylactic shock from which recovery seemed most improbable when the final blood sample was taken. The histamine content of the blood had risen from three to nine times its control value.

Since the guinea pig in severe anaphylactic shock suffers from an extreme degree of oxygen lack, it was possible that the anoxemia alone might account for the increased amounts of histamine in the blood. To check this possibility, a number of animals, of which the last three in Table I are representative examples, were placed in an atmosphere of pure nitrogen. Blood samples were taken before exposure to nitrogen and when respiratory movements had ceased as a consequence of exposure to the nitrogen. The blood histamine was, if anything, reduced.

It may be concluded that in severe anaphylactic shock in the guinea pig the histamine content of the blood is increased and that this increase is not due to the coincident anoxemia.

The results are in accord with the earlier studies on isolated perfused



organs. On the basis of Schild's<sup>61</sup> experiments, it seems likely that the increased quantity of histamine found in the blood of the intact guinea pig did not originate from a single organ but arose from tissues scattered throughout the animal. It may be concluded that in the guinea pig histamine is liberated during anaphylactic shock and that it plays a definite role in the symptomatology of the reaction in this species.

#### ANAPHYLAXIS IN THE DOG

Biedl and Kraus<sup>9</sup> in 1909, first described the two most outstanding features of anaphylactic shock in the dog, the fall of blood pressure and the reduced coagulability of the blood. The fall of blood pressure they thought was due to vasomotor paralysis caused by the formation of a toxic peptonelike substance. Good evidence of liberation of a circulating toxic substance appeared the following year when Manwaring<sup>38</sup> published the results of experiments carried out in the laboratory of the late Professor E. H. Starling at University College, London. Manwaring found by cross-circulation methods, that when a normal dog receives blood from a dog in anaphylactic shock, signs of anaphylaxis develop. In his experiments exclusion of the liver from the circulation of the sensitized dog prevented the occurrence of shock. His data indicated that the acute fall of blood pressure which occurs during anaphylaxis in the dog is due to the explosive liberation of depressor substances from the liver.

The importance of the presence of the liver in anaphylactic shock in the dog was corroborated and emphasized by the studies of Voegtlin and Bernheim<sup>64</sup> in 1911, and of Denecke<sup>20</sup> in 1914, and by a series of investigations by Weil<sup>66,67</sup>, and Weil and Eggleston<sup>68</sup> in 1917. The interpretation placed on the hepatic changes by Weil was not that originally stated by Manwaring. Because his experiments did not indicate the presence of toxic factors in the blood, Weil concluded that the fall of blood pressure in canine anaphylaxis was a secondary result of hepatic congestion. In the light of more recent findings, Weil's failure to demonstrate toxic substances in the blood seems most certainly to have been due to the methods used for detection. For similar reasons Manwaring and his collaborators<sup>39</sup> in 1925, were unable to detect depressor substances in blood from the carotid artery of dogs in anaphylactic shock. Nevertheless, in their experiments the blood from the liver did possess definite blood pressure lowering properties.

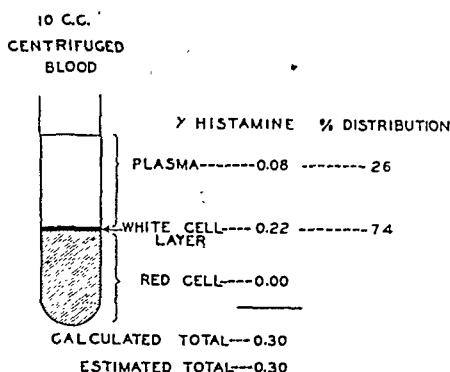
The problem rested in this somewhat confused state until the outstanding studies of Dragstedt and his associates<sup>21,22,23,24,29</sup> were reported a few years ago. They demonstrated the presence of a vasomotor substance in blood taken from the inferior vena cava just above the diaphragm. The site is important because the vein in this locality carries a good deal of blood which has come directly from the liver. Extensive investigation of the active substance by Gebauer-Fuelnegg and Dragstedt<sup>29</sup> in 1932, and by Dragstedt and Mead<sup>22</sup> in 1936, allowed them to

## MECHANISM OF REACTIONS—CODE

conclude that it was histamine. Like Weil<sup>67</sup>, and Manwaring and his associates<sup>39</sup>, Dragstedt and Gebauer-Fuelnegg<sup>21</sup> did not consistently find a vasomotor substance in blood from the femoral or carotid vessels.

The development of the Barsoum-Gaddum method for the quantita-

### THE DISTRIBUTION OF HISTAMINE IN THE BLOOD OF THE NORMAL DOG



### THE DISTRIBUTION OF HISTAMINE IN THE BLOOD OF THE DOG DURING ANAPHYLACTIC SHOCK

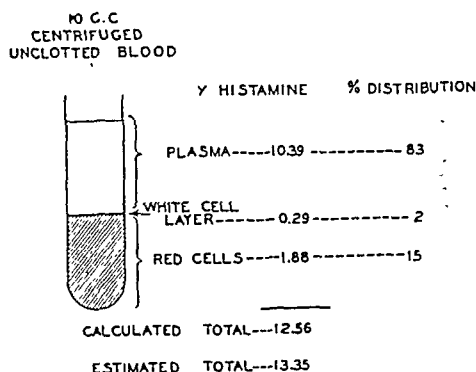


Fig. 3. (*left*) The distribution of the histamine in the blood of normal dogs. The total amount of histamine present is small, being only 0.3 microgram per 10 c.c. There is little histamine—indeed, often none—in the plasma. The white cell layer which separates out between the plasma and the red cells contains 74 per cent of the total present and is consistently the major source of the histamine in the blood of normal dogs.

Fig. 4. (*right*) The histamine in the blood of dogs taken during the early stages of a severe anaphylactic reaction. The total amount of histamine present is increased, being 13.4 micrograms per 10 c.c. The white cell layer has practically disappeared and the remnant accounts for only 2 per cent of the total present. The plasma contains 83 per cent of the histamine present and is thus the major source of the histamine in blood drawn under these conditions.

tive estimation of histamine in the blood has facilitated the investigation of this problem. The refinements accomplished by the method have allowed the estimation of quantities of histamine which would escape detection by earlier procedures. Using this technique the histamine concentration of the peripheral blood has been followed during anaphylactic shock of varying severity in more than twenty dogs (Code, 1939).<sup>15</sup>

Whenever the typical signs of anaphylactic shock developed, the concentration of histamine in the blood was increased from two to more than eighty times the control value. The rise in the blood histamine roughly paralleled the degree of shock displayed by the animal—being greatest when the reaction was severe and least during mild reactions.

In blood from normal animals most of the histamine is held within the white cells (Fig. 3). Before ascribing any of the symptoms of anaphylaxis to the increased quantities of histamine present in the blood, it was important to determine whether the additional histamine was in the plasma, free to produce its physiologic effects, or was held safely within the cells of the blood. The distribution of the histamine in centrifuged blood taken during the early stages of severe anaphylactic reactions was studied. The results were in striking contrast to those obtained with normal blood. The white cell layer had practically disappeared from the blood.

Some of the histamine had diffused into the red cells but its major source was the plasma, where it was free to produce its physiologic effects (Fig. 4).

In most experiments the histamine content of the blood was determined

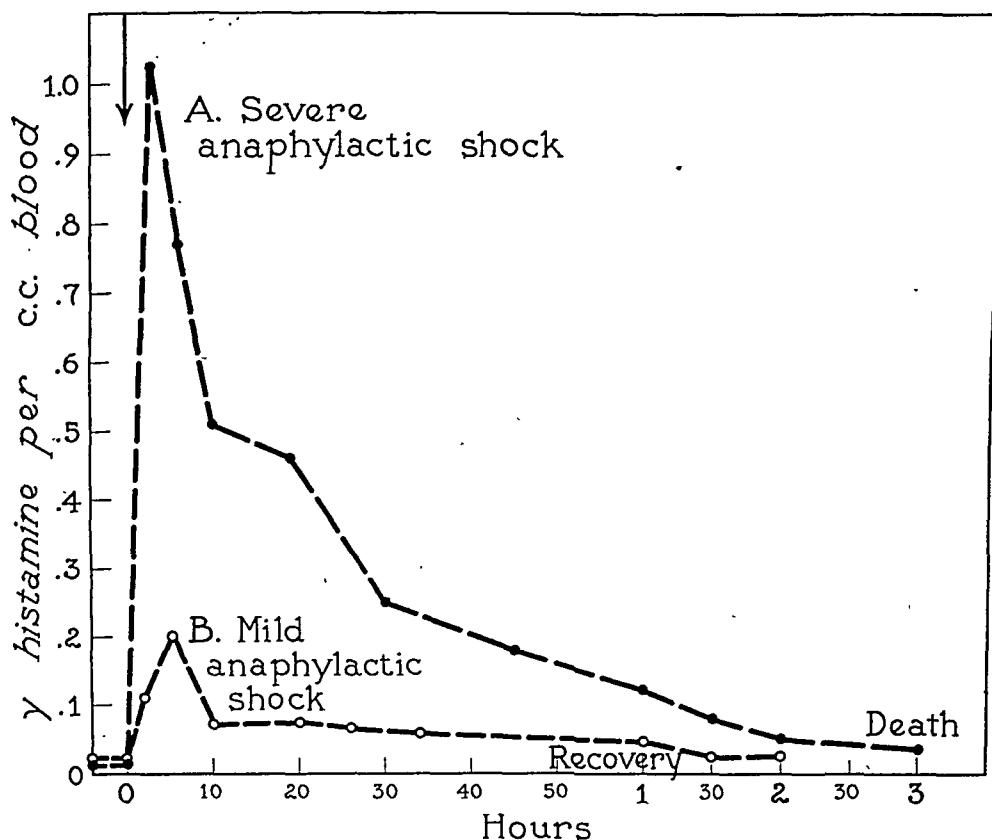


Fig. 5. (From C. F. Code, *Am. J. Physiol.*, 127:78-93, [Aug.], 1939. See page 83.) Blood histamine changes during a mild and a severe anaphylactic reaction in anesthetized dogs. At the arrow the antigen was given intravenously.

at frequent intervals for periods of one, two or three hours or more. The maximal concentration of histamine was generally reached within ten minutes after injection of the shock dose of antigen. After this initial rise the concentration fell rapidly, often returning to normal values in two to three hours (Fig. 5).

It was noted that this explosive liberation of histamine coincided with the dramatic fall of blood pressure which is such a prominent feature of anaphylaxis in the dog (Fig. 6). The amounts of histamine present in the blood were sufficient to account for the fall of blood pressure. The correlation between the fall of blood pressure and the rise of blood histamine was striking but it should not completely overshadow the observation that if the animal survived this initial period, the blood histamine quite rapidly returned to normal levels.

In my experience dogs die of anaphylaxis in either of two stages of the

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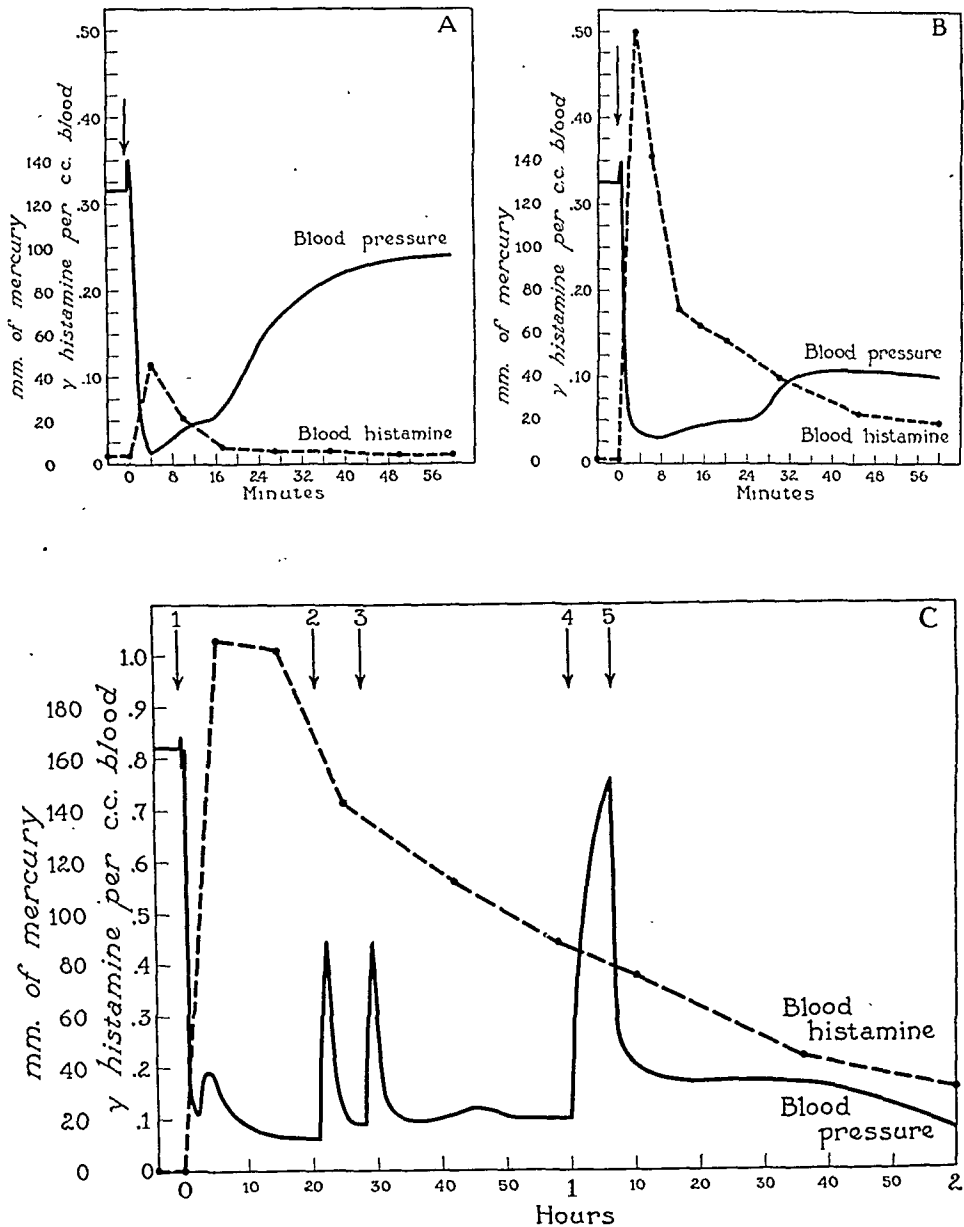


Fig. 6. (From C. F. Code, *Am. J. Physiol.*, 127:78-93 [Aug.] 1939. See page 87.) The blood pressure and blood histamine changes during anaphylactic shock in anesthetized dogs. At the first arrow in each experiment the antigen was injected intravenously. *A*, mild, anaphylactic shock; *B*, a more severe reaction; *C*, fatal reaction—seventeen minutes after injection of antigen the animal ceased breathing and blood pressure was less than 20 mm. of mercury; artificial respiration was commenced. At arrows 2 and 3 and between arrows 4 and 5, epinephrine and 10 per cent solution of glucose were given intravenously. With the continued high blood histamine these supporting measures were ineffective, the blood pressure did not increase and the animal succumbed a few minutes after the two-hour mark.

reaction. When the amounts of histamine liberated are sufficient, the circulation is flooded with this highly active capillary dilatant, in the presence of which the blood pressure cannot recover and death occurs early in the chain of events (Fig. 6C). The animal may, however, recover from this early phase of the reaction, the blood histamine returning to

normal values and the blood pressure recovering somewhat. Later some animals even with a normal blood histamine may sink into profound shock and coma and die with a normal blood histamine. While histamine seems quite clearly to be the cause of death in the early stages of the reaction, there is some difficulty in incriminating it as the lethal factor when its presence can barely be detected in the blood.

Also, while histamine can account for the sudden fall of the blood pressure during acute anaphylaxis in the dog, it does not account for the development of incoagulability of the blood, which is such a striking feature of the reaction in this species. Jaques and Waters<sup>32</sup> in 1941 showed that the blood fails to clot because heparin is liberated from the liver during the reaction. The preponderance of evidence definitely indicates that most of the histamine released during the reaction likewise comes from the liver (Watanabe<sup>65</sup>, 1931; Ojers, Holmes and Dragstedt<sup>41</sup>, 1941). It seems probable that histamine and heparin are liberated simultaneously as a result of a reaction or disruption within the hepatic cells.

The data suggest the following interpretation: first, that histamine is not the fundamental factor in anaphylaxis or in allergic reactions and that a deeper search into the etiology of this baffling condition must be made; second, that histamine is liberated as a consequence of damage done within the sensitized cells, and it is this damage to the cell that is the fundamental etiologic factor in allergic or anaphylactic reactions. Liberation of histamine may be purely incidental. If the damaged cell happens to contain histamine, it will be liberated during the reaction. It is unlikely that histamine produces the damage. Liberation of histamine may be a dramatic and indeed lethal factor if the quantities liberated are sufficient and if, as in the guinea pig, the animal is sufficiently sensitive to its effects. But, as has been pointed out, dogs may die hours after the increase of histamine in the blood has disappeared. Such animals, it seems likely, die as a consequence of the damage which, incidentally, liberated the histamine. Histamine is not the only substance liberated. In allergic reactions in the dog there are symptoms not only of histamine poisoning but also of heparin action. It seems probable that the fundamental mechanism of anaphylactic reaction lies in the process producing the damage within the cell, as a consequence of which these substances are liberated.

#### ANAPHYLAXIS IN THE RABBIT

Severe anaphylactic shock in the rabbit is accompanied by a fall of carotid blood pressure. Auer<sup>4</sup> in 1911 emphasized the role of the heart in the fall of the blood pressure. He noticed the pronounced dilatation of the right side of the heart during fatal reactions and he concluded that failure of the heart was the cause of acute lethal anaphylaxis in this animal. The work of Airila<sup>2</sup> in 1914, Coca<sup>11</sup> in 1919 and Drinker and Bronfenbrenner<sup>27</sup> in 1924 has clearly shown that during acute anaphylaxis

in the rabbit there is a pronounced increase of peripheral resistance in the pulmonary vascular bed due to contraction of the muscular coat of the pulmonary arterial tree and that this is the cause of the right-sided heart failure. Histamine injected into rabbits also causes pulmonary vascular constriction (Dale and Laidlaw<sup>19</sup>, 1910; Cloetta and Anderes<sup>10</sup>; Rocha e Silva<sup>55</sup>, 1940). Is the pulmonary vascular constriction of acute anaphylactic shock in the rabbit produced by histamine?

Rose and Weil<sup>60</sup> in 1939 and Rose<sup>56</sup> in 1940 showed that the blood histamine falls in anaphylactic shock in the rabbit. Can a reduction in the blood histamine possibly contribute to the symptoms of the reaction? The important question is: Where is the histamine in the blood—is it in the cells or in the plasma? In normal rabbit blood the major amount is present in the white cell elements. In severe anaphylaxis leukopenia uniformly occurs. In perfusion experiments using lungs and blood from sensitized rabbits, Dragstedt and associates<sup>25,26</sup> have demonstrated that on addition of the sensitizing protein to the blood, 50 per cent of the white cells drop out of the circulation during their first passage through the lungs, and at the same time the histamine content of the blood is reduced (Dragstedt, Ramirez de Arellano and Lawton<sup>25</sup>, 1940; Dragstedt, Ramirez de Arellano, Lawton and Youmans<sup>26</sup>, 1940).

What happens to the histamine in these white blood cells during the reaction? The white blood cells of the rabbit are rich in histamine (Code and Ing<sup>16</sup>, 1937). Can they, like other cells, participate in the reaction? Katz<sup>33</sup> in 1940 showed that the cells of sensitized rabbits' blood do react. He withdrew blood from sensitized rabbits, added the antigen and incubated the mixture for twenty minutes. The plasma from this "shock" blood contained two to six times as much histamine as plasma from the same blood tested in a similar fashion but to which no antigen had been added. Dragstedt and co-workers in 1940<sup>25</sup> and 1941<sup>30</sup> and Rose<sup>57</sup> in 1940 confirmed this observation. Rose has given a good example of the experiment.<sup>57</sup> In a control sample of blood from a sensitized rabbit, 85 per cent of the histamine was in the white cell layer. In the "shock" blood from the same animal incubated with antigen 80 per cent was found in the plasma. As Abell and Schenck<sup>1</sup> showed in 1938, the physical properties of white blood cells are altered in rabbits during anaphylactic reactions. In the test tube, during the shock reaction the white cell elements of the blood are altered or damaged and their histamine is released into the plasma.

Although the whole blood histamine may fall during anaphylaxis in the rabbit, the amount liberated from the white cells would be sufficient to produce a marked constriction of the pulmonary vessels. Again in this species it seems that histamine produces the pronounced and often lethal symptom of the reaction, but again cells have been damaged and it is suggested that search into this cellular disruption must be made if the fundamental factors in anaphylaxis are to be unearthed.

## COMMENT

Some profit may be derived from a discussion of certain features of allergic reactions of human beings in the light of facts and conclusions derived from animal studies. Here I must tread lightly because my experience is limited and the clinically trained reader is much better fitted to lead one into this maze than I.

First, what are the routes through which a sensitizing agent may normally enter the body? They are (1) the skin and conjunctiva; (2) the upper portion or the pulmonary portion of the respiratory tract and (3) the gastro-intestinal tract. Once the agent has passed these surface structures, it will be in the blood stream and thence may reach any of the body tissues.

What tissues of the body commonly display allergic reactions? There seems little doubt that allergic reactions are most commonly observed in the tissues listed at the external surfaces of the body, the tissues which since man's beginnings have been brought in contact with sensitizing agents. They might be termed the barrier tissues—barring the way of sensitizing agents to deeper, more vital structures. All of the surface tissues display allergic reactions. All so far tested contain histamine (Best and McHenry<sup>8</sup>, 1931). Does histamine contribute to the symptoms produced in an allergic reaction in these tissues?

Histamine has three major physiologic actions. It acts (1) on smooth muscle to produce contractions; (2) on capillaries to produce dilatation and increased permeability, which may lead to formation of edema and (3) on secretory glands as a secretagogue. The acute phases of allergic reactions in many tissues seem adequately explained on the basis of liberation of histamine. In the lungs, for example, histamine acting on smooth muscle to produce bronchiolar constriction, on capillaries to produce edema and on the mucus glands to produce mucus, could quite accurately reproduce the findings of asthma. But the evidence is purely indirect.

In the skin, the urticaria and wheals of an acute reaction may also be duplicated by injection of histamine (Lewis and Grant<sup>37</sup>, 1924). More direct evidence, however, is available. Katz<sup>34</sup> in 1942 devised a method whereby he can test for the liberation of histamine during local allergic reactions in the skin. With patients showing a skin reaction to the intradermal injection of ragweed, he observed a sharp increase of output of histamine from the skin into which the antigen had been injected. The studies of Rose<sup>58</sup> in 1941 on the blood of patients suffering from dermatographia and cold allergy have shown that during formation of extensive wheals histamine may be liberated from the skin and appear for brief periods in increased quantities in the blood. Once again histamine is associated with the acute phases of the allergic reaction. Its role at the surface of the body may be the production of a wheal in an attempt to limit the further entrance of the sensitizing agent. But what of the fate

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of the damaged surface cell from which the histamine was liberated? Is it not possible that in certain types of chronic dermatitis we observe this battered cell—so often damaged by repeated allergic onslaughts that it bears little resemblance to its former self, so often damaged that it can no longer give standard cutaneous reactions?

Of the tissues within the body, the blood is by far the most accessible and as a consequence has been the most carefully studied. Haworth and MacDonald<sup>31</sup> in 1937 compared the concentration of histamine in the blood of seventy-five card-room workers suffering from cotton-dust asthma with that in the blood of 103 university students and eighteen persons suffering from chronic bronchitis. The concentration of histamine in the blood of the asthmatic group was normal or slightly greater than normal, with an average value for the group a little greater than that of the university students and the chronic bronchitic patients. Repeated observations were made in a number of instances on the students and on the asthmatic patients. The histamine content of the blood of the normal students remained remarkably constant while that of the asthmatic patients showed marked fluctuations.

Rose<sup>59</sup> in 1941 confirmed these findings and extended them to other allergic conditions. His series included patients suffering from asthma, urticaria, angioneurotic edema, eczema and vasomotor rhinitis. The concentration of histamine in the blood of these patients was usually normal or slightly elevated. In some cases, during acute attacks there was a definite reduction of the blood histamine level, particularly in cases of angioneurotic edema. With the exception of patients having urticaria, all tended to have fluctuating blood histamine values compared with the constant levels noted among normal subjects. It seems likely that the histamine content of the blood of patients suffering from these allergic conditions is usually within the normal range but it tends to fluctuate widely in contrast to the constant values usually found among normal persons. The most that can be said from these data is, it seems, that in certain allergic conditions histamine metabolism is disturbed.

But the whole blood histamine is simply the reflection or the mean of a variety of possible changes in cells containing histamine scattered throughout the body. The blood itself contains such cells. Katz and Cohen<sup>35</sup> in 1941 showed that the cells of the blood of patients sensitive to ragweed, timothy or horse dust liberate histamine when exposed *in vitro* to the specific allergen. The blood cells of the allergic human being are similar in this respect to those of the sensitized rabbit, guinea pig and dog (Katz, 1940).<sup>33</sup> Apart from blood and skin cells, do cells elsewhere in the body liberate histamine during allergic reactions? There is no direct evidence that this occurs in man.

The red bone marrow contains histamine (Code and Jensen, 1941)<sup>17</sup> and it may be involved in the reaction of serum sickness (leukopenia, agranulocytosis). But tissue need not contain histamine to react. The



central nervous system, particularly the brain, contains little or no histamine (Kwiatkowski, 1943)<sup>36</sup>; yet it most certainly may be involved in severe reactions.

## CONCLUSIONS

Thus, for the present the following conclusions may be tentatively drawn:

1. Histamine is released during acute allergic reactions as a consequence of damage to cells already containing histamine.
2. Its release from such cells is rapid and explosive and the histamine may be in sufficient quantity to kill the animal. However, if the animal survives, the histamine soon disappears. When the histamine has disappeared, there may still remain the damaged cell.
3. Cells which do not contain histamine may suffer damage as a consequence of an allergic reaction and the damage may produce symptoms—even death.
4. Thus, in allergic reactions histamine may produce a dramatic and often distracting veil of symptoms behind which lies the damaged cell. The mechanism of that damage to the cell is the challenge to allergists today.

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## THE MECHANISM OF DESENSITIZATION

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**T**YPICAL anaphylaxis occurs only under artificial circumstances, when relatively large doses of antigen are willfully introduced at a relatively rapid rate, more or less directly into the circulation of animals sensitized by the parenteral exposure to the same antigen, many (not less than seven or ten) days previously.

If, instead, these animals receive a relatively small test dose of antigen, or even if a larger dose is given in high dilution or injected slowly,<sup>†</sup> or if the injection is made only a short time (not more than three to four days) following initial (or the last serial) exposure, the acute anaphylaxis does not occur, although (depending on the size of the test dose) the animals may show characteristic symptoms of subacute anaphylaxis of varying degrees of severity. Moreover, such animals, after a prompt recovery, may now withstand the rapid injection of several times the test dose of antigen which would have certainly killed them if it were so given in the first place.<sup>2,3</sup>

This refractory state, called a "state of antianaphylaxis" by Besredka, is only relatively effective (it may be overcome at any stage by increasing the test dose of antigen). This refractoriness lasts for a relatively short time (hours or days), depending on the amount of antigen injected, after which the reactivity returns; that is, the animal is again capable of responding to small doses of specific antigen with the original intensity.

At first glance this temporary refractoriness might suggest that "sensitivity" of the animal has decreased or has been abolished and, because this refractory state was produced by injection of specific antigen, it looks as though the antigen has combined with or exhausted the available antibody. It is for this reason the phenomenon is currently referred to as "desensitization."

This term is highly misleading and has been instrumental in obscuring the true facts by suggesting (as many investigators hold even today) that the level of antibody determines the type of the reaction of the animal to the antigen. In fact, Topley and Wilson<sup>49</sup> summarize this view as follows:

"The balance of experimental evidence is strongly in favor of the view that the anaphylactic response is the result of an antigen-antibody reaction occurring on or in the cells that have removed the antibody from the blood and in some way fixed it themselves. The anaphylactic state is associated with the presence of

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<sup>†</sup>Lewis, J.A.M.A., 76:1342, 1921.

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fixed antibody and the absence of circulating antibody. The immune state is associated with the presence of circulating antibody in a concentration sufficient to protect the fixed antibody that is also present."

Similarly, Wells<sup>52</sup>, in discussing the nature of the antianaphylactic state, says: "This term should logically be applied only to a resistance due to antibodies." In short, according to this concept, when test dose of antigen is injected into the animal possessing an excess of circulating antibody, the latter combines with the antigen and prevents it from reacting with cellular antibodies, and thus the tissue injury and resulting symptoms are prevented.<sup>22</sup>

While it is true that guinea pigs may be rendered hypersensitive (to some antigens at least) by a single, relatively small preliminary injection, presumably resulting in the production of limited amount of antibody, this is not true generally. For instance, in order to elicit any signs of hypersensitiveness in rabbits, dogs, and particularly in monkeys, these animals must receive many injections of antigen over a period of many days "until considerable amount of antibody has appeared in the blood<sup>55</sup>," and they do not exhibit symptoms of hypersensitiveness while antibody content is low. Similarly, man is relatively infrequently sensitized by a single exposure to antigen; as a rule hypersensitiveness develops only as a result of repeated exposures continued over a relatively long period of time.

Furthermore, if it were true that excess of circulating antibody protects the sensitized tissue, it should follow that through repeated injection of antigen over a period of hours (as it is done to prevent shock in connection with serum therapy in hypersensitive individuals), more and more of the circulating antibody should be bound and thus, at the later stages of this process, the tissues should be more and more likely to react with the antigen. Actually, the reverse is true; the more antigen is injected (in gradually increasing amount), the more solid is the resistance to shock from the subsequent injections of antigen.

It is true that under different circumstances (as in the attempts to free the patient suffering from hay fever of their symptoms) where patients receive a number of injections of antigen continued over a long period of time, they actually *do* develop additional amounts of circulating antibodies by the time they become refractory ("desensitized"). It is commonly stated that these previously "hypersensitive" individuals are made "immune" (do not suffer from exposure to the allergen), but the evidence that this freedom from symptoms is directly referable to the acquisition of additional antibody is, to say the least, not convincing. Indeed, if production of an excess of antibody were the essential (necessary and sufficient) means of producing refractoriness (or antianaphylactic state), how could one account for the fact that previously hypersensitive animals become antianaphylactic immediately following injection of a single large (but sublethal) dose of antigen (as in guinea pigs), or immediately following the completion of a series of injections of small

(increasing) amounts of antigen given within a few hours (as in the case of human beings hypersensitive to therapeutic serum). These procedures certainly do not involve the immediate production of additional antibody. In fact, the production of antibody following these injections becomes detectable only several days later; but by the time additional antibody actually appears, the state of refractoriness has disappeared and the original hypersensitiveness has usually returned.

That high concentration of circulating antibody does not protect the animal against anaphylactic shock is best illustrated by the well-known observation that immune animals with high antipolysaccharide antibody content in their blood (so high that a fraction of a cubic milliliter of their serum will passively protect mice against many thousand lethal doses of pneumococcus), are killed by anaphylactic shock if a mere trace of specific polysaccharide in solution is injected intravenously.

The erroneous notion that excess of circulating antibody protects the animal against anaphylaxis by preventing the antigen from reaching the sensitized tissues has its origin in the experiments of Friedberger<sup>22</sup>, further strengthened by Weil.<sup>51</sup> This author found that injection of additional antibody into the circulation of previously sensitized guinea pigs rendered them refractory to antigen.<sup>51</sup> However, his conclusions as to the mechanism of this refractoriness have since been found to be wrong. As found in my laboratory by Dr. Morris<sup>37,38</sup>, the refractoriness of animals in Weil's experiments was due, not to excess of antibody as such, but to the fact that he introduced the antibody in the form of foreign (rabbit) serum.\* The effect would have been exactly the same if, instead of immune rabbit serum, he would have injected normal rabbit serum (or even more effectively, normal fowl or horse serum) immediately preceding the test injection of antigen.<sup>20,27,31</sup> Our own unpublished experiments (1915), later confirmed by Morris<sup>38</sup>, have shown that if the antibody is derived from a homologous animal, if the antibody is collected late in the process of immunization to avoid the presence in it of traces of antigen, and if from twenty minutes to one hour is allowed to elapse between the injection of additional antibody and the injection of antigen (so as to allow time for a nonspecific "anaphylactoid" effect of injection to be dissipated), the animals receiving additional antibody actually are more hypersensitive than the controls. That is, the anaphylactic shock can be elicited in the former animals with a considerably smaller test dose of antigen than in the latter (controls).

From the preceding discussion, it seems clear that excess of circulating antibody does not produce the state of refractoriness or antianaphylaxis. It is evident, therefore, that the effectiveness of "desensitization" through a properly conducted (single or repeated) exposure to antigenic stimulation must involve some other mechanism.

\*Friedberger<sup>22</sup> pointed out still another source of error to be guarded against in such experiments—the additional serum injected into sensitized animals may contain traces of antigen and thus may render recipient antianaphylactic as a result of the reaction between this antigen and the recipient's antibody.

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The definition of the basic difference between the state of immunity and that of hypersensitiveness, as quoted from Topley and Wilson<sup>49</sup>, suggests at least one other possible mechanism. In fact, in an earlier edition of the book,<sup>48</sup> these authors have specifically stated that, as a corollary to the view that fixed antibody is present in both the hypersensitive and immune animals, and that the latter (immune) owe their lack of hypersensitiveness to the presence of an excess of antibody in the circulating blood, one is justified in inferring that<sup>48</sup>,

"... a 'hypersensitive' animal may be desensitized in two ways: by receiving a small dose of antigen, so administered to neutralize the fixed antibody without precipitating acute shock, or by receiving repeated doses of antigen so spaced and graduated as to give rise to a high concentration of antibody in the circulating blood."

There is no doubt that hypersensitive animals can be made refractory to antigen either by a single or by multiple exposure to sublethal (or gradually increasing) doses of antigen. However, we have seen that the production of additional antibody is not the mechanism responsible for this effect.

Let us now consider the second mechanism that has been suggested<sup>48</sup>, namely, that hypersensitive animals may be rendered refractory by saturation of the sessile antibodies.

In discussing the "desensitization" as being the result of saturation of cellular antibody, Zinsser<sup>53</sup> suggested that, "the animal so treated (properly desensitized) for a time, loses its capacity to react with antigen in a manner analogous to chemical saturation." This hypothesis is not open to direct verification since we know of no methods for quantitative evaluation of the cellular antibody.

It is quite conceivable that in such animals in whom hypersensitiveness exists without demonstrable circulating antibody, the antigen, which is injected for the purpose of "desensitization," would combine directly with the sessile antibodies and might conceivably, under special conditions, saturate them. However, in such animals in whom excess of circulating antibody is present, no such direct union with cellular antibody can be expected. (In fact, the other half of the hypothesis actually postulated the preferential anchoring of the antigen by the circulating antibody and resulting prevention of its union with cellular antibody.)<sup>48</sup> Thus, if saturation of cellular antibody were essential for establishment of the state of refractoriness, the "desensitization" of animals possessing excess of circulating antibody would be expected to be impossible, or at least more difficult to attain.

Since in actual experience desensitization *does* occur in such animals (and with usual doses of antigen), in spite of the presence of circulating antibody, and since such "desensitized" animals still possess enough free antibody left over (so that a small amount of their serum may sen-

sitize normal homologous animals), it would seem necessary to postulate that, if in "desensitized" animals antigen has united with sessile antibody, the antigen must possess a greater affinity for sessile antibody. Realizing this and other difficulties in trying to correlate respective significance of the cellular and humoral antibodies, Weil<sup>51</sup> actually stated that "the only solution appears to lie in the assumption of an increased 'avidity' of the anchored antibodies, as compared with the free antibodies, for the antigen."

But if this auxiliary hypothesis is accepted, then it is clear that the definition of an immune state<sup>49</sup> as depending on preferential union of antigen with the circulating antibody, thus preventing it from reaching the sensitized tissues, must be abandoned.

In short, the suggestion of a dual mechanism as given by Topley and Wilson<sup>48</sup> for accomplishing "desensitization" is untenable because it contains an internal contradiction—the two mechanisms are mutually exclusive and cannot be offered as component part of one hypothesis.

In considering the second part of the hypothesis by itself—namely, that "desensitization" is due to exhaustion or saturation of the sessile antibody<sup>53</sup>, one is confronted immediately with several facts which contradict it. In the first place, no matter how effectively an animal is "desensitized" (presumably because its sessile antibodies have been saturated), such animal can be thrown into anaphylactic shock by an injection of a large dose of antigen. The "desensitization" is never complete, but only relative. If the cells have lost their power to unite with moderate amount of antigen, how can they react with a larger one?

Moreover, when animals are simultaneously sensitized to two or more antigens and receive a "desensitizing" injection of one of them, they become more or less refractory to all other antigens at the same time. True, the solidity of this nonspecific antianaphylaxis in the *in vivo* experiments, was claimed by many investigators to be less marked against heterologous antigens<sup>41,24</sup>; also *in vitro*, Dale observed "that uterus of a guinea pig sensitized against two different antigens and then desensitized completely to one of them, loses a certain amount of sensitiveness to the other."<sup>15</sup> However, other investigators found that desensitization to all antigens was approximately equal in solidity.<sup>4,5,21,36\*</sup> It is clear that under these circumstances, the refractoriness must be due to some mechanism other than saturation of specific antibodies in the tissues.

It is clear that refractoriness of these animals to antigens other than the one with which these animals have been "desensitized" cannot possibly be due to the specific saturation of sessile antibodies.

The notion that sessile or fixed antibodies play a decisive role in the mechanism of anaphylaxis has its origin in early experiments in which it was found that a certain amount of time (several hours) was necessary

\*Some unpublished experiments carried on in my laboratory many years ago, have indicated that this discrepancy could be eliminated if animals used for such experiments were uniformly sensitized (that is, if instead of active sensitization one employed a passive sensitization with a uniform amount of antibody), if the antibody were derived from homologous animals, and if the antigens used for test injections were carefully standardized before the test and the doses injected were equivalent in their anaphylactogenic potency.

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before the passively sensitized animal was able to react to a test injection of the antigen.<sup>40†</sup> In spite of the fact that in the rabbit, dog and mouse<sup>34,35</sup> passive anaphylaxis could regularly be elicited by injection of antigen immediately after introduction of a sensitizing serum (as well as by an injection of a mixture of antigen and antibody into normal animals, including guinea pigs)<sup>25</sup>, the relative irregularity in the results of such experiments when performed in guinea pigs (in whom allowing for an incubation period between passive sensitization and test injection, seems to contribute to a greater regularity of results), was responsible for the postulate that incubation period for the "fixation" of antibody was essential.

However, more recently, even some of those investigators who previously insisted on the particular significance of the incubation period, (which was necessary for the fixation of antibody by the tissues in guinea pigs), have found that passive anaphylaxis can be produced in guinea pigs without allowing any "period of incubation."<sup>16,54</sup> Moreover, in the experiments performed *in vitro* with red blood cells<sup>17,28,29</sup>, and with strips of uterus and small intestine<sup>32</sup>, it was found that union between antigen and antibody occurring in the environment into which normal red cells or tissues, respectively, are introduced, causes an injury resulting in the liberation of histamine from these normal cells without incubation period.

Such considerations as these suggest that, while actively sensitized animals undoubtedly possess fixed tissue antibody, the assumption that in passively sensitized animals the tissue becomes reactive *only* when and if antibody becomes fixed to the tissues is not well founded. Moreover, these findings make very doubtful the validity of the hypothesis that "desensitization" is accomplished by saturation of fixed antibodies.\*

This discussion was intended to make clear that the term "desensitization" is a misnomer. The temporary relative refractoriness of a hypersensitive animal, achieved through the administration of a suitably chosen dose (either single or multiple) of antigen does not decrease the basic specific sensitivity of the animal. In fact, though not immediately, it tends to increase it. Moreover, this temporary refractoriness is secured neither by the interposition of circulating antibody between the antigen and sensitive cells, nor by the saturation of fixed antibodies. Apparently the refractoriness is determined by some other mechanism entirely outside of antibody balance.

That the state of refractoriness must rest on a different mechanism than *true* desensitization is evident also from other considerations.

Mention has already been made of the fact that the refractoriness resulting from exposure of multiply sensitized animals to one of the respec-

†Doerr and Russ: *Ztschr. f. Immunitäts., Orig.*, 3:181, 1909; Manwaring: *Ztschr. f. Immunitäts., Orig.*, 8:1, 1910-11; and Weil, J.: *Med. Res.* 28:85, 1913.

\*The latter conclusion, however, cannot be stated more definitely until such time when it is shown experimentally that normal uterine strips exposed to such mixtures of antigen and antibody become refractory to a subsequent exposure to similar mixtures.



tive antigens will render these animals (or isolated tissue)<sup>15</sup> relatively refractory to any other antigen to which they happen to be simultaneously sensitized. Thus, while in this instance, the process of establishing the refractory state is specific, that is, it depends upon the introduction of a particular antigen to which specific sensitivity exists, the resulting effect of the refractory state is *not* specific—the animal exhibits diminished reactivity to the effects of introduction, not only of this particular antigen, but also of any other antigen to which the corresponding antibody is also present.

On the other hand, occasionally a diminution in reactivity of a sensitized animal to the injurious concomitant effects of antigen-antibody union (refractoriness to anaphylaxis) has been observed to occur spontaneously (without any "desensitization"), as for instance in allergic individuals suffering or recovering from measles, scarlet fever, cancer, or during pregnancy, etc. Furthermore, a state functionally very closely resembling the refractory or antianaphylactic state may be produced at will artificially by a parenteral introduction of a great variety of substances (other than specific antigens). As a group, these substances (antigenic or nonantigenic *per se*, organic or inorganic) are characterized by the fact that they are capable (by virtue of their inherent toxicity) of eliciting anaphylaxis-like ("anaphylactoid") reactions when injected into normal animals.

The pathological changes found as result of injection of anaphylactoid agents are strikingly similar to those found in anaphylaxis and more recently (particularly in the case of peptone<sup>19</sup> and trypsin)<sup>42,43,44,45</sup>, it was found that both these changes and the symptoms observed in anaphylactoid reactions are due to the liberation of histamine, the mechanism which is strongly suspected of being responsible for similar changes in true anaphylaxis.

However, while this resemblance is very strong, the two phenomena differ from each other in some minor respects due unquestionably to the secondary effects of the individual properties of the different anaphylactoid agents employed, the effects which are superimposed over the basic reactions. For this reason, while admitting the major resemblances, some of the investigators are cautious in drawing conclusions as to their significance. Thus, for instance, Topley<sup>47</sup>, in discussing the resemblance between "anaphylactic" and "anaphylactoid" reactions, states:

"... The resemblances are certainly striking and it seems that common factors are involved; but there are certain differences."

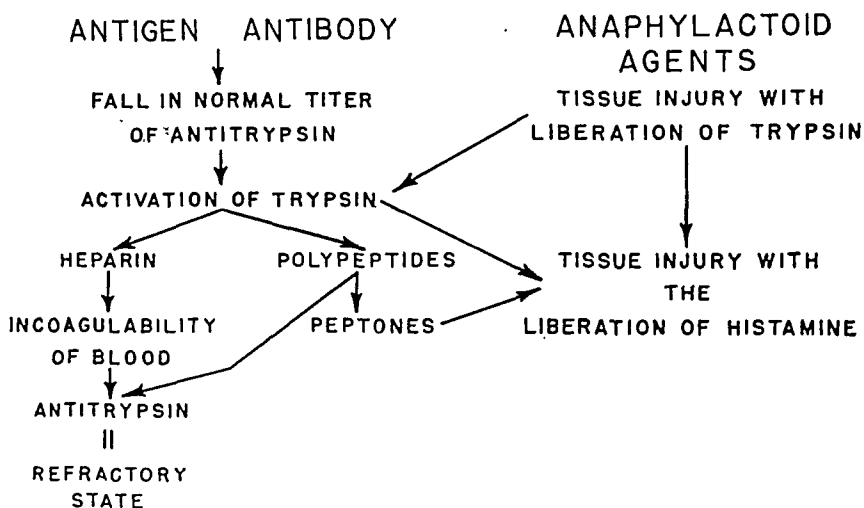
"... The resemblance is not due to any similarity in the underlying mechanism, but to the fact that, in each case, cellular injury is followed by the liberation of histamine."<sup>50</sup>

On the other hand, to many investigators, these resemblances seem very significant. Thus Hanzlick<sup>26</sup>, on the basis of his extensive study of anaphylactoid reactions, came to the conclusion that the mechanism involved

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in these reactions is basically related to that which operates in true anaphylaxis.

About thirty years ago, before the role of histamine in anaphylaxis was definitely suggested, we found that the products of interaction of antibody with antigen *in vitro* resulted in the activation of serum trypsin



and subsequent autodigestion of serum.<sup>6</sup> Either trypsin itself, or the products of its action (both of which are present in the mixture), when injected into animals produced symptoms indistinguishable from anaphylaxis.<sup>8</sup> We found also that serum properly absorbed with kaolin or starch *in vitro* has similarly caused activation of serum ferments<sup>12</sup>, with subsequent autodigestion of the serum, which became capable of producing anaphylaxis-like symptoms when injected intravenously, especially in homologous animals.<sup>9,10</sup>

These early findings receive support and are considerably more meaningful now that it has been found that either reaction of antigen-antibody as such, or trypsin (or some products of its activity) are capable of setting free performed histamine from the erythrocytes<sup>28,29</sup>, skin<sup>30</sup>, or smooth muscle<sup>42</sup> *in vitro*, and thus presumably also *in vivo*.

Furthermore, some of these early findings have also suggested what I think is the true mechanism responsible for the refractory state.

As the serum-tryptase becomes activated (through physico-chemical changes initiated by the antigen-antibody union)<sup>9\*</sup>, the products of its digestive activity have a tendency to delay or even arrest further activity of the enzyme.<sup>11</sup> They exert so-called "antitryptic" activity.<sup>1</sup> Some of these products have been identified more recently as polypeptides.<sup>30</sup> Undoubtedly other constituents of the serum (as, for instance, normal serum albumin<sup>7</sup>, unsaturated fatty acids<sup>†</sup>) and products appearing during

\*See also Dale, H. H.: *Lancet*, 1:1285, 1929.

†Schwartz: *Wien. Klin. Wchnschr.*, 22:1151, 1909; Bauer, J. Z.: *Zeitschr. f. Immunitäts.*, 5:196, 1910; Jobbling, J. W., and Petersen, W.: *Jour. Exp. Med.*, 19:239, 251 and 459, 1914.

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the reaction *in vivo* (for instance, heparin)<sup>18,33</sup>, are also capable of inhibiting the activity of trypsin. Some of these substances, spoken of collectively as "antitrypsin" are not dialysable; thus, once a high antitrypsin content is established, it may persist for some time. We have shown that irrespective of the method by which a rise in antitrypsin was produced—whether specifically (as a result of antigen-antibody reaction)<sup>12</sup>, or non-specifically by (injection of anaphylactoid agents)<sup>13</sup>, the animals remain refractory to anaphylaxis so long as the antitryptic titer remains elevated.<sup>11,14,46</sup>

The refractory state, therefore, does not involve the antibody balance but seems to be due to the fact that the environment (in the general circulation or at the cell surface) is so changed by the presence of trypsin-inhibitors (antitrypsin) that any subsequent liberation of trypsin finds the medium unsuitable for its activity, and hence no further liberation of histamine (due to the tissue injury caused by trypsin itself, or by some of the toxic products of its activity) takes place.

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### HISTAMINE TOLERANCE

By R. Katzenstein, M.D.

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Corroborative evidence of acquired tolerance to histamine by the dog is presented. Additional studies of canines with such acquired tolerance were made to ascertain any possible resultant structural changes and its functional manifestations. These observations included high altitude reactions and changes in the ketosteroid content of the urine. A brief review of the increased tolerance to histamine by guinea pigs and dogs as shown by Horton and his associates and Karady is presented. This type of functional disturbance is distinguished from tachyphylaxis: a rapid adaptation to small doses of histamine, observed by Karady and by Eichler and Killian. The latter were able to inject 150 mg. of histamine into rabbits without producing their death if done within a half hour after a preliminary small injection. The structural changes following histamine death when the latter occurs sufficiently late (twenty-four hours) vary from necrobiosis of cerebral or cerebellar ganglion cells to cerebral infarcts without vascular occlusion. Other lesions observed due to lack of tolerance are peptic ulcer of the stomach and duodenum, adrenal cortex hemorrhage and marked passive congestion of the viscera, particularly the liver.

#### Experimental Study

An initial dose of 1 mg. of histamine for a dog of  $10 \pm$  kg. slowly increased by successive injections over a protracted period protected the animal from death when a single injection of 50 mg. was made. In seven of eight dogs subjected to this procedure only minor anatomical changes were demonstrable. The author noted that the increase in the amount of histamine tolerated becomes limited with successive doses and that structural changes are more likely to result when symptoms of the more severe type occur while developing tolerance.

A second group of thirteen animals received single or repeated doses of sufficient amounts of histamine to cause severe and protracted symptoms. There was a marked contrast in the results obtained compared to those receiving histamine tolerance doses. The histamine shocked group manifested extensive lesions of the heart, central nervous system and alimentary canal. The most constant changes occurred in the heart with yellow mottling seen from the epicardial and endocardial surfaces as well as the cut surfaces of the myocardium, due to focal accumulations of fat with their necrosis and peripheral collections of mononuclear cells. Early lesions of the alimentary canal were edema, congestion and hemorrhage of the mucosa and submucosa. Later changes are followed by focal necrosis with ulceration. Focal hyaline necrosis of the spleen was most frequent in this organ, although anemic and hemorrhagic infarcts may be observed.

Tachyphylaxis was also observed when recording the blood pressure following small doses of histamine. There were no changes of symptoms and the animals quickly recovered from a single dose of 6 mg. per kg. which would prove fatal in ten minutes for untreated dogs.

Tachyphylaxis also did not cause hypertrophy of the adrenal cortex as it does in the rat.

Two groups of animals were subjected to varying high altitudes, up to 41,000 feet above sea level, in checking both normal controls and histamine-tolerant dogs. Dr. L. F. Nims, who aided in the high altitude experiments, expressed the criteria of the reaction of the dogs to the high ceiling by indicating that the respiration rate increased proportionately to the decreasing atmospheric pressure. There was no appreciable difference observed in the "respiratory ceiling" or the urinary 17 ketosteroid content of the histamine tolerant and the control animals.

# MOLD FUNGI IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASES

## III. Immunological Studies with Mold Extracts

### 1. Preparation of Experimental Extracts

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CLINICAL experiences with extracts prepared by The Association of Allergists for Mycological Investigations have been confusing. While in many instances diagnostic reactions have been obtained with high dilutions, most of us have become skeptical lest the use of higher concentrations has resulted in an unwarranted number of falsely positive tests. Such nonspecific reactions possibly could incriminate certain of our extracts as being both impotent and irritative. In 1942, Browning<sup>1</sup> reported on the mathematical evaluation of our extracts and confirmed the impression that this irritative-type of reaction is entirely too frequent with many of them.

At the Little Rock meeting of our group in 1942, it was, therefore, decided that more effort be devoted to a study of various methods of preparing mold extracts with the object of obtaining more efficient and less irritating antigens.

Our routine method of extract preparation has been described elsewhere.<sup>3</sup> Briefly, the pellicles are grown to maturity on a standard malt extract broth (Difco), harvested, washed with several changes of normal saline to remove whatever irritants might be contained in the culture medium, and dried to constant weight at 40° C. Some early extractions were made in buffered saline but a modified Hollister-Stier extracting fluid was substituted in 1940, in the hope that more permanent antigens could be obtained. Extracts prepared in this manner on a weight-volume ratio of 1:20 are still in use, and in the following remarks will be referred to as extracts prepared by the usual method. The Hollister-Stier solution has been modified by the addition of "Merthiolate" (Lilly), to a concentration of 1:10,000 by weight.

If we are to condemn our extracts as irritative or impotent, let us consider the possible sources of error in their preparation. In the first place we have subjected these wet mold pellicles to a slow-drying process and have proceeded from there just as we work with such better known antigens as pollens. About 1939, Nelson suggested that in slow drying, the pellicles might undergo an irreversible hardening process somewhat

<sup>1</sup>From the Department of Botany and Bacteriology, The University of Texas, in collaboration with The Association of Allergists for Mycological Investigations.

<sup>2</sup>Assisted by a Grant in Aid from the Alumni Research Fund of the Society of the Sigma Xi.

<sup>3</sup>Read at a meeting of The Association of Allergists for Mycological Investigations, St. Louis, Missouri, January 21, 1944.

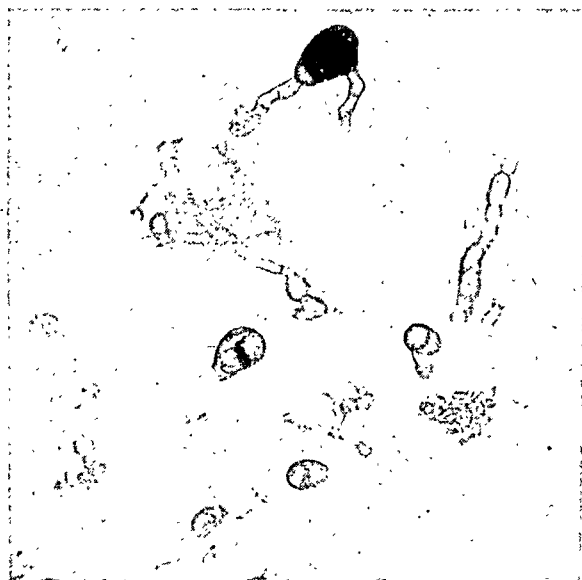


Fig. 1a

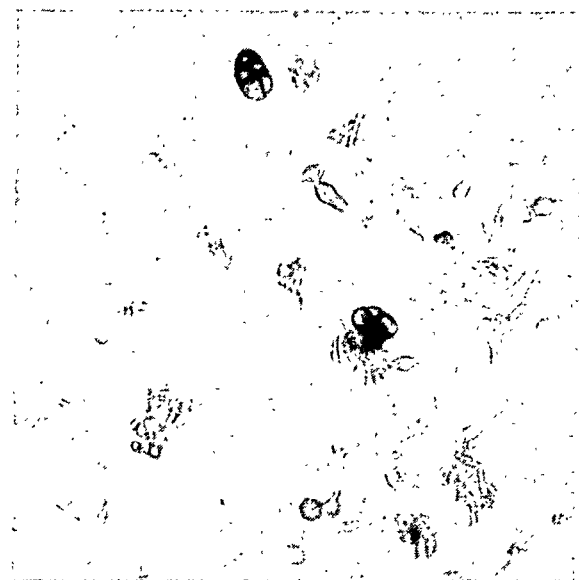


Fig. 1b

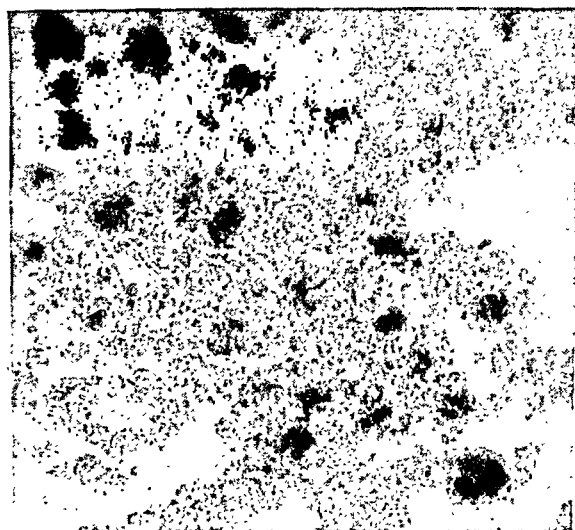


Fig. 1c

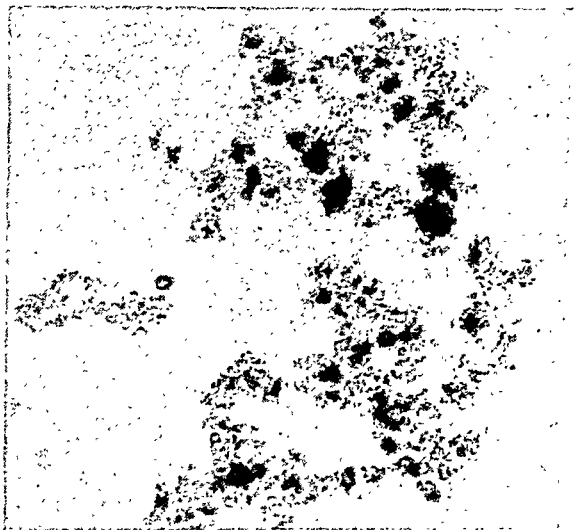


Fig. 1d



Fig. 1e

Fig. 1. Photomicrographs of *Alternaria tenuis* Nees BC-17, prepared for extraction by various methods.

(a) Dried by lyophilization. (b) Dried by lyophilization and defatted. (c) Dried by lyophilization, defatted and ground. (d) Dried by lyophilization and ground. (e) Dried to constant weight at 40°C., according to the usual method.

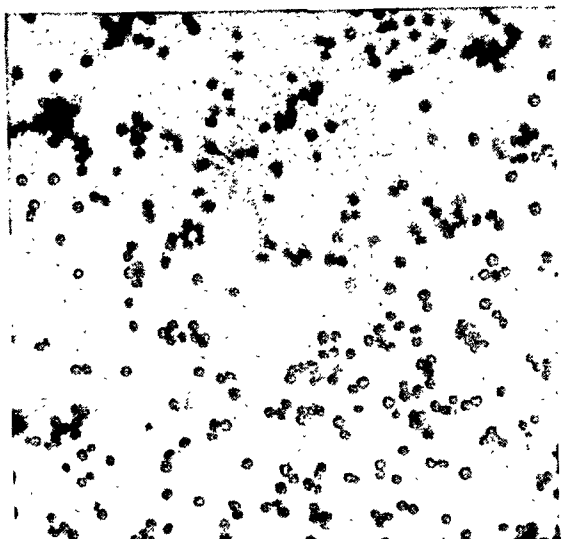


Fig. 2a

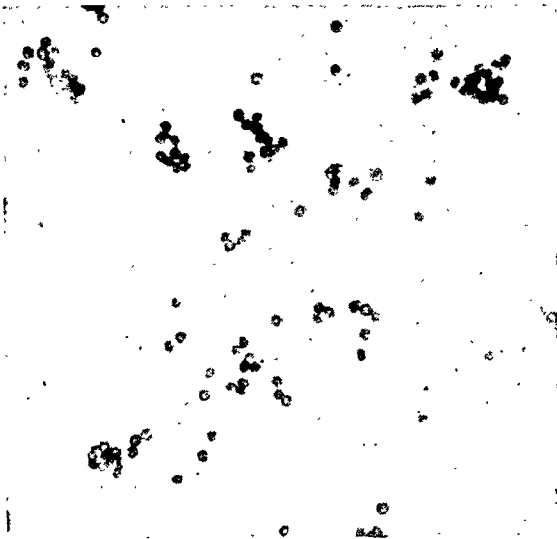


Fig. 2b

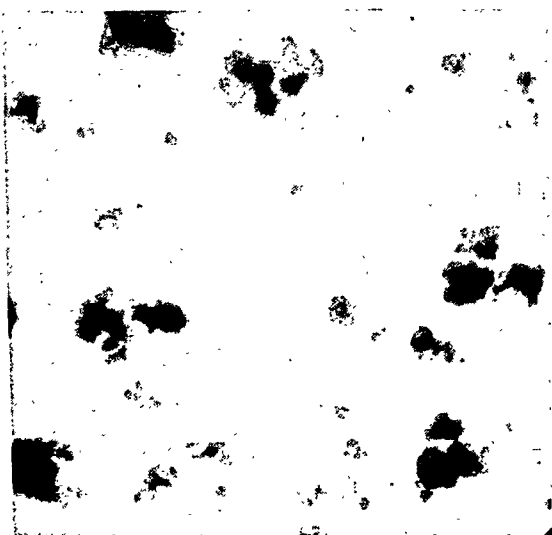


Fig. 2c

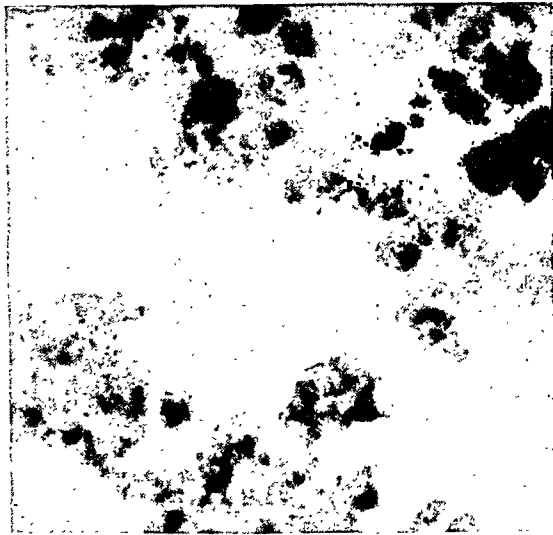


Fig. 2d

Fig. 2. Photomicrographs of *Aspergillus niger* BC-70, prepared for extraction by various methods.

(a) Dried by lyophilization. (b) Dried by lyophilization and defatted. (c) Dried by lyophilization, defatted and ground. (d) Dried by lyophilization and ground. (e) Dried to constant weight at 40°C., according to the usual method.

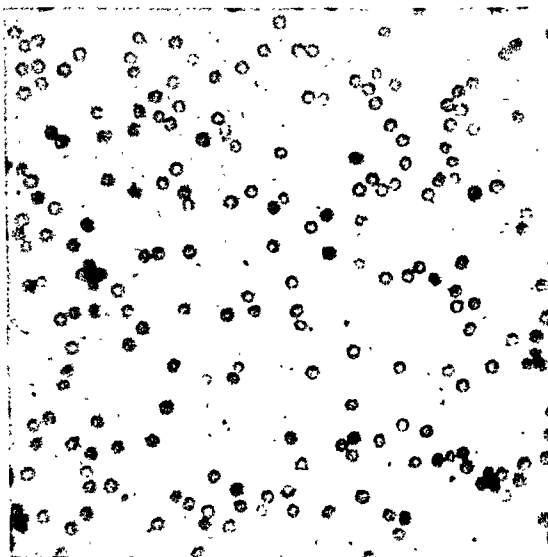


Fig. 2e



comparable to coagulation, whereby the active principle might either become altered or at least not again freely soluble in water.

Again some controversy has arisen regarding just wherein the active principle is contained in molds. While no definite proof has been forthcoming to show that allergens in the spores and mycelium are identical, most workers feel that more active material actually is contained in the spores than in the mycelium<sup>2</sup> and, therefore, have assumed that if they could produce more spores they could make better extracts. Sometime in the spring of 1942, Dr. G. W. Goldsmith, of the Department of Botany and Bacteriology of the University of Texas, mentioned to us and Wittich, that some previous work on mold spores had revealed intracellular molecular concentrations sometimes approximating 275 atmospheres of pressure. He suggested, furthermore, that the higher concentrations would be expected in smaller, more spherical spores, such as those of *Penicillium* and *Aspergillus*, and conversely that larger spores like *Alternaria*, *Helminthosporium* and other members of the *Dematiaceae* group could have less intracellular concentration. From a practical standpoint, this suggests that it would be difficult or even impossible to extract active principles from within the spores, especially those of the higher molecular concentrations, provided the spore walls actually were tough enough to present an obstacle, and provided, further, the spore walls were not ruptured prior to or during the process of extracting. From these considerations it occurred to us that we might have an explanation of why we have been able to produce apparently more active extracts from the *Dematiaceae* molds than from some of the others, such as species of *Aspergillus* and *Penicillium*. In a few instances one of us (Prince) has observed apparently definite, reliable skin tests from extracts of certain species of *Aspergillus* and *Penicillium*, but such cases are certainly not nearly as frequent as one would expect to encounter, considering the widespread distribution of these mold forms. We have often wondered if the few significant reactions obtained with *Aspergillus* and *Penicillium* could not have resulted from antigenic material extracted from the mycelium rather than from the spores.

The matter of defatting antigenic material before extraction has given rise to some argument. However, there seems to be a rather general consensus of opinion that pollens yield better extracts if previously subjected to removal of waxes and lipoids by fat solvents. We have wondered, therefore, just what significance defatting would have in the preparation of mold extracts. Except for a few experimental extracts which were not systematically studied, our routine pellicles have not been defatted. Furthermore, it is a known fact that mold material often contains a high percentage of lipoids, up to approximately 40 per cent in some species.

With the object of investigating these three major considerations, a

## RESPIRATORY ALLERGIC DISEASES—PRINCE AND MORROW

series of experimental extracts was begun in the spring of 1943, using molds planted in malt extract broth in November, 1942. The flasks containing the mature pellicles with maximum sporulation were shaken vigorously to dislodge the pellicles from the surface of the broth, and the broth was decanted through filter paper. The pellicles were washed with 20 successive changes of normal saline in amounts equivalent to approximately the volume of the original broth. With these washings each flask was shaken vigorously and the saline allowed to stand on the pellicle a few minutes. To convenient portions of the broth and of the fourth, tenth, fifteenth, and twentieth washings was added 1:10,000 "Merthiolate" and these portions saved for future study. After the last washing the pellicles were cut in thin strips, frozen rapidly between cakes of dry ice and dried by lyophilization. All containers were sealed immediately after drying to prevent reabsorption of moisture from the air.

The dried pellicles were then divided into four portions. The first portion was not further treated. The second portion was defatted with anhydrous ethyl ether in Soxhlet equipment protected by calcium chloride to prevent absorption of moisture from the air. The third portion was similarly defatted and ground in a porcelain ball mill with smooth flint pebbles for several days. The fourth portion was placed immediately into the ball mill without preliminary defatting. All transfers of the dried material from one container to another were made in a dehydrator cabinet. This precaution was instituted after previous work had revealed that lyophilized material is quite hygroscopic and rapidly takes up considerable moisture in ordinary air. A fifth portion of pellicle was prepared by the usual method of slow drying. From these variously treated pellicles, five extracts were prepared simultaneously in Hollister-Stier fluid containing 1:10,000 "Merthiolate" on a weight-volume ratio of 1:20 and sent out to the members of our group in October, 1943. The extracts prepared by the first four methods were designated by number only, but the members were informed that extract five was prepared by the usual technique.

To recapitulate, these extracts were prepared as follows:

1. Dried only by lyophilization
2. Dried by lyophilization, defatted
3. Dried by lyophilization, defatted, ground
4. Dried by lyophilization, ground
5. Usual method (slow drying)

Two different molds were selected for these various methods of extract preparation—the two being *Alternaria tenuis*, Nees, and *Aspergillus niger*, Thom and Church. *Alternaria* was selected because so far it seems to be the most prevalent mold with which most of us are familiar, and because it seems to be a frequent troublemaker among the molds. *Aspergillus*, on

the other hand, was selected for just the opposite reason; it has not been associated frequently with respiratory allergy, even though it is widely distributed. The members were asked to make serial dilutions from 1:100 to at least 1:100,000 and to perform testing both on known *Alternaria*-sensitive and possibly *Aspergillus*-sensitive patients, and on patients not considered sensitive to either of these molds.

The photomicrographs of the variously treated mold material (Figs. 1 and 2) reveal that spores and mycelium of both the *Alternaria* and the *Aspergillus* were very thoroughly broken up in the ball milling process. We were quite surprised to note that this was true regardless of whether the pellicles had previously been defatted; we had anticipated difficulty in grinding the undefatted material. A very definitely darker color was observed in both the *Alternaria* and *Aspergillus* extracts prepared by Method 3, in which the pellicles were dried by lyophilization, defatted and ground.

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2. Pratt, Henry N.: The comparative atopic activity of *alternaria* spores and mycelium. *J. Allergy*, 13:227, 1942.
3. Prince, Homer E., and Morrow, Marie B.: Air-borne molds in the etiology of respiratory allergic diseases. *Tri-State M. J.*, May, 1939.

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REACTIONS TO PARENTERAL FLUID ADMINISTRATION. Strumia et al: *Ann. Int. Med.*, 19:718, (Nov.) 1943.

The various causes for reactions are discussed. Classification includes: (1) Causative agents inherent in fluid alone (pyrogenic, nitritoid, embolic and mechanical). (2) Inherent qualities of fluid combined with condition of patient. Included here are hemolytic and allergic—latter reactions attributed to substances, alimentary in origin, contained in whole blood, plasma or serum to which the recipient is sensitive. Localized urticaria is usually present, but may be generalized and associated with angioneurotic edema and rise in temperature. Asthma is occasionally seen. The danger of edema of the glottis must be considered, since it occurs in 0.3 to 1 per cent of all transfusions. It should be insisted that the donor be fasting. Reactions respond well to epinephrine. True anaphylactic reactions are rare. (3) Conditions inherent in recipient alone (hyperhemolysis, liver disease, hypoproteinemia, cardiac insufficiency). (4) Temperature, air emboli, free hemoglobin, etc.

L. J. H.

MANAGEMENT OF PAROXYSMAL TACHYCARDIA INCLUDING THE USE OF MECHOLYL. Morgan, P. W.: *Ann. Int. Med.*, 19:780, (Nov.) 1943.

Mecholyl (acetyl-beta-methylcholine) causes a bronchial spasm abolished by epinephrine or by atropine. It is contraindicated in the treatment of paroxysmal tachycardia for those patients who also have bronchial asthma.

L. J. H.

## MOLD FUNGI IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASES

### III. Immunological Studies with Mold Extracts

#### 2. Skin Tests with Experimental Extracts

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SKIN testing with extracts prepared by the various methods for this study has been performed on patients sensitive to *Alternaria* and on individuals not considered to be sensitive to *Alternaria*. While several testing records are complete with intradermal titrations in strengths from 1:100,000 to 1:100 including scratch testing using 1:20 concentration for all five extracts, intradermal tests with 1:1,000 dilutions have been most frequently performed and will of necessity form the basis of this report. In some instances definitely positive reactions have been obtained with 1:10,000 or 1:100,000 dilutions but have not been carried out in higher concentrations. On the other hand, many testing records revealed that observations only in concentrations of 1:100 had been made, or that the 1:1,000 strength had not been used for both *Alternaria* and *Aspergillus*, or the records were in some other detail incomplete and could not therefore be incorporated into this report.

Table I shows the results of intradermal testing on fifteen patients with respiratory allergy in whom sensitization to *Alternaria* was considered a major, although not necessarily the only, etiological factor. Only in Cases 7, 8 and 9 were definite reactions consistently obtained with *Aspergillus niger*. The patient in Case 7 was considered definitely sensitive to *Aspergillus niger* and patient 8 was considered probably sensitive to *Aspergillus niger*. Both patients in Cases 7 and 8 had *Aspergillus niger* included in their therapeutic mixtures. Patient 9 had not been considered sensitive to *Aspergillus niger* in spite of the fact that he reacted fairly consistently with the various experimental extracts. No differences can be observed which might be attributed to any variation in preparation of the experimental extracts, nor as distinguishing the experimental from our ordinary type of extract. The latter statement is further borne out by the test records of "other" extracts which are in all instances routine preparations previously supplied the various investigators; in case 4 the extract was made from dried pellicles of *Alternaria* prepared in our routine fashion and supplied to the investigator for his own extraction; in Cases 9, 13, 14 and 15 the testing antigen was a pool of our *Alternaria* extracts; in Cases 7 and 8 the extracts of *Alternaria tenuis* and *Aspergillus niger* were

Presented before the Association of Allergists for Mycological Investigations, St. Louis, Missouri, January 21, 1944.

TABLE I. INTRADERMAL SKIN TESTING WITH EXPERIMENTAL EXTRACTS 1/1000 IN PATIENTS IN WHOM ALTERNARIA IS A MAJOR ALLERGEN.

Meth- od	ALTERNARIA TENUIIS							ASPERGILLUS NIGER					INVESTIGATORS	Season				OTHER IMPORTANT ALLERGENS
	1	2	3	4	5	Other	1	2	3	4	5	Other		Winter	Spring	Summer	Fall	
Case 1	++	+	?	++	++		-	-	-	-	-		KDF Asthma Hay fever	x	x	x	x	Ragweed
2	++	+++	+	+	++		-	-	-	-	-		KDF Asthma Hay fever	x	x	x	x	Ragweed, dander
3	+++	-	+	+	?		-	-	++	++	-		KDF Asthma	x	x	x	x	
4	+++	++	++	+++	++	++	-	-	-	-	-		KDF Asthma Hay fever	x	x	x	x	
5	+++	++	+	++	++		-	-	-	-	-		KDF Asthma	x	x	x	x	Dust, ragweed, grass, wheat
6	++	?	+	++	+		?	?	+	?	?		KDF Asthma	x	x	x	x	Ragweed, grass, dust, dander
7	+++	+++	+++	+++	+++	++	++	++	++	++	++	++	FWW Asthma	x	x	x	x	Pollens
8	+++	++	++	+++	+++	++	++	++	++	++	++	++	FWW Asthma Hay fever	x	x	x	x	Pollens, foods
9	++	++	+	+	++	++	+	+	+	++	+		HEP Asthma Hay fever	x	x	x	x	Ragweed, grass, dust
10	-	+	+	+	+		-	++	-	+	-		EDS Asthma	x	x	x	x	Pollens, dust
11	?	+	++	+	++	+	?	-	?	-	+		HEP Asthma	x	x	x	x	Ragweed, dander, dust, food
12	+	++	+	++	++		+	+	-	?	+		HEP Hay fever	x	x	x	x	Ragweed, dust, grass
13	++	++	++	++	++	++	+	?	+	+	?		HEP Asthma	x	x	x	x	Dust, grass
14	+	++	+	++	++	++	+	+	+	?	-		HEP Hay fever	x	x	x	x	Dust, ragweed, hickory
15	++	++	+++	+++	+++	++	-	?	?	?	?		HEP Asthma Hay fever	x	x	x	x	Ragweed, dust, grass

Capital X indicates that in the season specified, the patient's symptoms are increased.

TABLE II. INTRADERMAL SKIN TESTING WITH EXPERIMENTAL EXTRACTS 1/1000 IN INDIVIDUALS NOT CONSIDERED PRIMARILY SENSITIVE TO ALTERNARIA.

Meth- od	ALTERNARIA TENUIIS							ASPERGILLUS NIGER					INVESTIGATORS	Season				OTHER IMPORTANT ALLERGENS
	1	2	3	4	5	Other	1	2	3	4	5	Other		Winter	Spring	Summer	Fall	
Case 1	-	-	-	-	-		-	-	-	-	-		HEP Asthma	x	x	x	x	Asp. terreus, Asp. nidu- lans, chronic bronchitis
2	+	++	+++	+	-	++	+	?	-	++	+	+	PTP Asthma	x	x	x	x	Dust, ragweed, marsh

## RESPIRATORY ALLERGIC DISEASES—FIGLEY ET AL.

[illegible]

Capital X indicates that in the season specified, the patient's symptoms are increased.

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routine distributions at an earlier date. Finally, differences in the reacting abilities of the various patients are maintained throughout most of the tests, irrespective of the modification of the particular extract.

Table II shows the results of intradermal testing with 1:1,000 dilutions in twenty-four patients in whom *Alternaria* sensitization was not considered of primary importance. The first twenty patients have respiratory allergies, while the last four are non-allergic.

A few interesting facts regarding the first three patients in this series might be mentioned. In Case 1 the patient did not react by scratch or by intradermal tests in all concentrations to either *Alternaria tenuis* or *Aspergillus niger*. However, in previous routine testing he had reacted to nothing except *Aspergillus nidulans* and *A. terreus*, in dilutions of 1:1,000, and therapy with these molds produced a good result. In Case 2 the patient had a very reactive skin which responded to practically everything with which he was tested, especially to cow hair, house dust and feathers. In Case 3 the patient reacted only to dust and ragweed in addition to *Alternaria*, but since he has been perfectly relieved on a dust and ragweed regimen without the employment of molds in his therapy, the mold reactions are not taken to indicate major sensitizations in his present environment. In Case 4 *Alternaria* was considered by the investigator to be of secondary clinical importance. In Cases 5 through ten, inclusive, molds were considered by the investigators to be of questionable importance, while in the remaining ten of the allergic patients they were considered entirely unimportant.

As in the first group, there are no outstanding differences in this series that might be attributed to any variations in the preparation of the experimental extracts.

### CONCLUSIONS

The observations herein presented as well as other unpublished data do not indicate any differences in any of the experimental extracts of *Alternaria tenuis* and *Aspergillus niger* that could be attributed to variations in the technique of preparation. Furthermore, the experimental extracts are about as active as extracts of the same materials prepared by our usual methods.

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### A CASE OF ASPIRIN POISONING—M.D. Charters. Brit. M. J., 1:10, (Jan.) 1944.

Case report of a patient who had taken 750 gr. aspirin in a suicidal attempt. Toxic signs began to appear about fourteen hours after taking the drug. Pyrexia was mild. Hyperpnea was marked and probably due to acidosis, resulting from either direct action of the acid radical of the drug or from the disordered metabolism. Disorientation was the only mental reaction. Toxic hepatitis resulted. Recovery of the patient is reported, with the excretion of the drug continuing over a period of at least four days.

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## MOLD FUNGI IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASES

### III. Immunological Studies with Mold Extracts

#### 3. Failure to Find Histamine-Like Substances in the Washings and Extracts of Molds Used for Skin Testing

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ALTHOUGH the significance of molds as allergic excitants of hay fever and asthma has been well established, the value of skin tests in determining mold antigens has often been questioned. Browning<sup>2</sup> has recently summarized results on a large number of extracts made available to members of the Association of Allergists for Mycological Investigation. In a series of thirty-eight extracts tested intracutaneously, he reported that 37 per cent were irritants and had no clinical value. Prince<sup>14</sup>, likewise observing marked reactions with certain of these extracts, has also expressed the opinion that some appear to be of the irritative class. On the other hand, Harris<sup>12</sup>, using different extracts and testing intracutaneously, found an incidence of 38.5 per cent positive *Alternaria* reactions in 130 patients with seasonal hay fever and asthma; his observations were reported to be statistically significant and to indicate that the extracts were nonirritative. Similar observations have been reported by Feinberg<sup>8</sup>, who also expressed much faith in skin testing, particularly on the scratch-test basis and with concentrated extracts or dry powder.

Realizing that the technique of preparation might be responsible for the irritating properties of some mold extracts, it was decided to assay the broth and washings of several fungi, together with their extracts, for histamine-like substances. When one recalls that histamine is widely distributed in the tissues of plants, as well as animals, and that it was first identified by Barger and Dale<sup>1</sup> in a fungus, *Claviceps purpurea* (ergot), its presence in mold extracts should not be surprising. Furthermore, the various broths on which the experimental molds are grown usually contain peptone, which, when contaminated by certain bacteria, is converted to histamine, as was shown some years ago by Hanke and Koessler<sup>11</sup>, and more recently by Roske.<sup>17</sup>

#### SOURCE OF MATERIAL, METHODS OF GROWING, AND PREPARATION OF EXTRACTS

Two molds, *Alternaria tenuis*, and *Aspergillus niger*, were selected as suitable materials for the tests reported here. Various surveys by Feinberg and Little<sup>9</sup>, Durham<sup>6</sup>, and Morrow, Lowe and Prince<sup>13</sup>, have indicat-

Presented before the Association of Allergists for Mycological Investigations, St. Louis, Missouri, January 21, 1944.



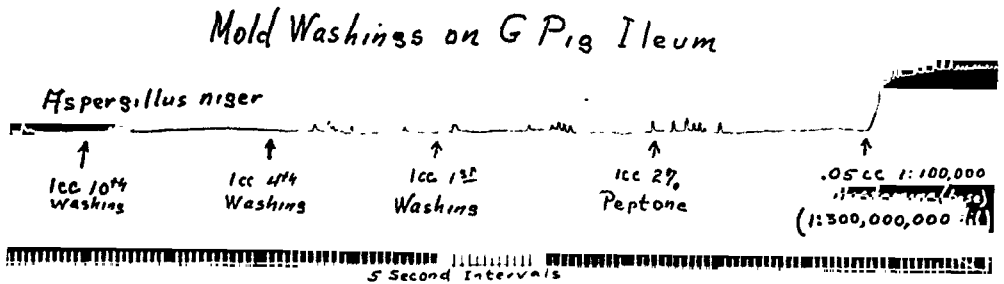


Fig. 1. A typical record showing the ineffectiveness of washings of *Aspergillus niger* and the effectiveness of minute amounts of histamine on the guinea-pig intestine. (In this and subsequent figures "1st washing" is used synonymously with "culture broth").

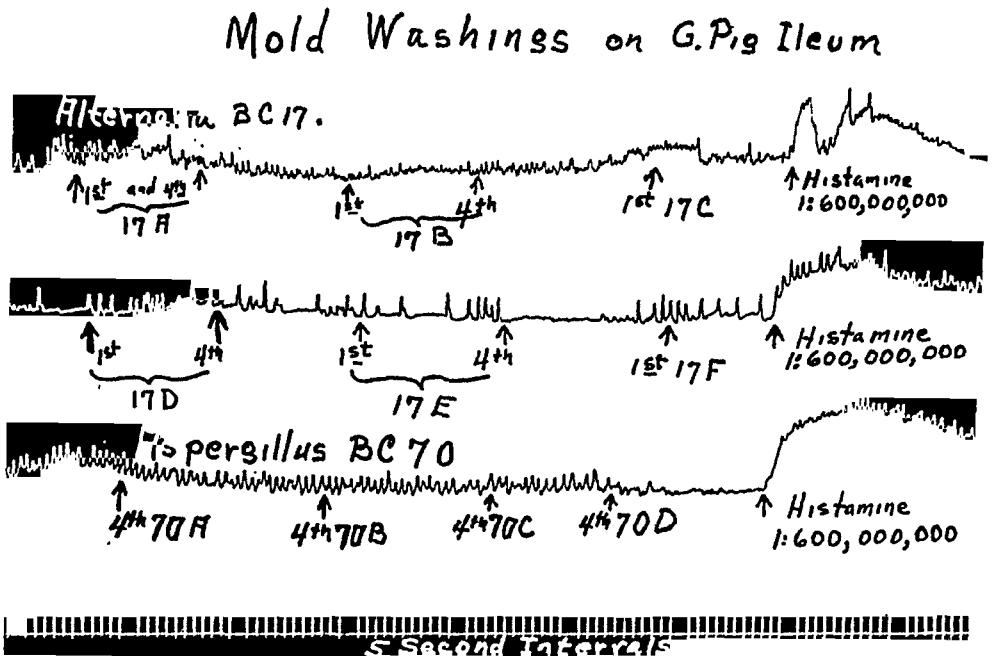


Fig. 2. Group testing of *Alternaria* BC-17 (*A. tenuis*) and *Aspergillus* BC-70 (*A. niger*). The letters A, B, C, D, et cetera, after numbers 17 and 70 refer to different preparations of the same mold.

ed that *Alternaria* and *Aspergillus* are widely distributed and are among the most frequent air-borne molds causing inhalant allergy. Feinberg<sup>7</sup> found that *Alternaria* gives positive skin reactions more frequently than other fungi, with yeast second and *Aspergillus* a close third. With the *Alternaria* group of extracts made available to members of the Association of Allergists for Mycological Investigations, Browning<sup>2</sup> found 29 per cent positive skin reactions in 979 patients; Chobot, Dundy and Schaffer<sup>3</sup>, using other extracts, observed 28.2 per cent positive reactions in 117 cases. With extracts of the *Aspergillus* group, Browning reported 23.7

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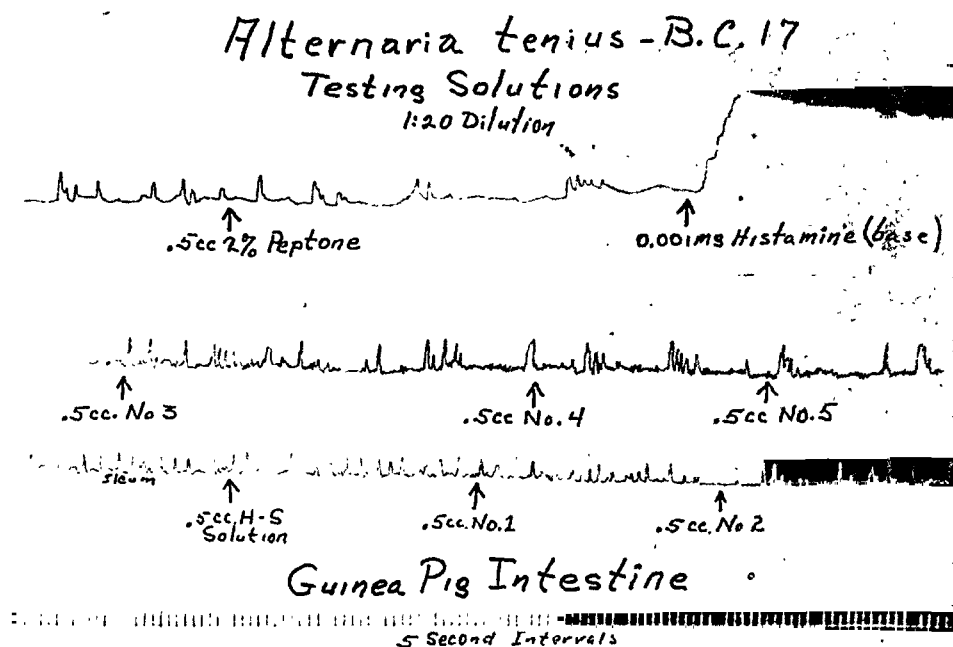


Fig. 3. The ineffectiveness of five mold extracts of *Alternaria tenuis* prepared by different methods of extraction. Record begins at lower left. "H-S" refers to the Hollister-Stier extraction fluid.

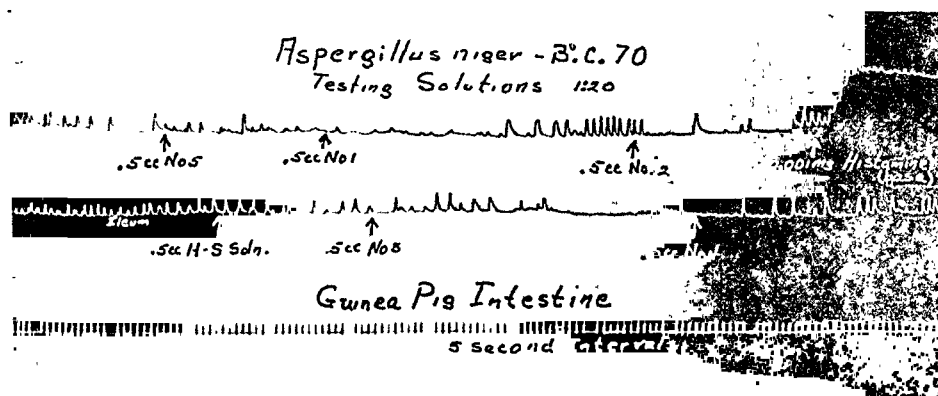


Fig. 4. The ineffectiveness of five mold extracts of *Aspergillus niger* prepared by different methods of extraction. Record begins at lower left. "H-S," Hollister-Stier extraction fluid.

per cent positive reactions in 1,092 patients; Chobot and his associates reported 16.1 per cent in 117 cases.

The source, distribution and identification of these molds have been described by Morrow, Lowe and Prince.<sup>15</sup> The general procedures employed in growing, harvesting and preparing extracts of these molds have been described by Prince and Morrow.<sup>15</sup> In the preparation of the present extracts, five different methods were used; these have been discussed in a preceding paper.

## RESPIRATORY ALLERGIC DISEASES—SELLE

*Testing for Histamine by the Guinea-pig Method.*—The methods employed were essentially those originally described by Schultz<sup>18</sup> and modified by Dale.<sup>5</sup> Each solution was tested on an isolated uterine horn or a segment of intestine (ileum) obtained from a half-grown guinea pig. The strips of smooth muscle were immersed in oxygenated Ringer's solution adjusted for a pH of 7.4 and maintained at a temperature of 30° C. until used. When testing, the strips were suspended one at a time in 150 c.c.

TABLE I. HISTAMINE SENSITIVITY OF TWENTY-SEVEN NORMAL SUBJECTS

Response to 0.02 c.c. Intracutaneously		
Concentration	Number Positive Reactions	Per Cent Positive Reactions
1:50,000	27	100
1:100,000	24	89
1:500,000	12	44
1:1,000,000	3	11
1:5,000,000	0	0

of Ringer's solution kept at 38° C. by thermostatic control and oxygenated by a constant stream of air. This stream of air also made possible a rapid and uniform mixing of any solutions added to the bath. After the test tissue had remained in the bath for a period of five to ten minutes, 1 c.c. of the tenth washing of the mold in question was added. Two to three minutes later, 1 c.c. of the fourth washing was added. This was followed after comparable intervals by 1 c.c. of broth (or first washing) and finally by a similar amount of 1 per cent peptone. The method employed in testing the mold extracts was essentially the same as that described for the washings and broth; however, the volume of extract added to the bath was 0.5 c.c., rather than 1.0 c.c.

The solutions were first tested separately on fresh muscle segments and finally, for sake of comparison, with other solutions of a similar nature on the same target tissue. On a separate test basis, each solution was examined at least four times, some more often, as slight spontaneous changes in tone or activity, which always occur even under ideally controlled conditions, were occasionally found to develop after addition of the solution. To rule out the possibility of positive responses, the solutions were rerun several additional times until unequivocal results were obtained.

Having examined the solutions separately, each of the five extracts for any one mold preparation was tested with similar extracts on the same muscle segment. It was thought that slight differences in histamine content might be detected by this procedure which would not be evident otherwise. By varying the sequence of addition, each extract was com-

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pared with other extracts, similar in source but differing in method of extraction, on a common target tissue.

The sensitiveness of the target tissue was finally demonstrated in each instance by characteristic smooth muscle contractions produced by the addition of 0.05 c.c. or 0.1 c.c. of a 1:100,000 dilution of histamine to the bath. In most instances, the tissue responded to the smaller amount of histamine, which represented a bath dilution of 1:300,000,000. In case of doubtful responses to the solutions tested or poor responses to the standard histamine-solution, the test was repeated on fresh tissues.

*Testing for Sensitiveness of Skin to Histamine.*—In order to determine whether or not the normal human skin might respond to amounts of histamine too minute to give positive reactions by the guinea-pig method, normal subjects, ranging in age from five to fifty years, were tested intracutaneously with 0.02 c.c. of the following histamine (base) solutions: 1:50,000, 1:100,000, 1:500,000, 1:1,000,000, 1:5,000,000. Physiological saline, with which the histamine solutions were prepared, was used as a control. Reactions were read and recorded according to Cooke's classification for intracutaneous testing.

### RESULTS

*Schultz-Dale Technique.*—While the addition of a given solution was occasionally followed by a change in tone or temporary decrease in activity, such a change was shown to be spontaneous and not due to constituents of the solution. Questionable responses were not duplicated on re-examination.

The results indicate that the tenth, fourth, and first washings (or broth) of the various molds were uniformly negative as regards their ability to cause characteristic histamine-like contractions of the uterus or intestine. Likewise, the addition of concentrated (1:20) mold extracts, prepared by the five different procedures, failed uniformly to produce specific reactions.

*Skin Tests with Histamine.*—The response of normal individuals to intracutaneous injections of histamine varied markedly. While none of the twenty-seven subjects reacted to a dilution of 1:5,000,000, three (11 per cent) responded to 1:1,000,000; twelve (44 per cent) responded to 1:500,000, twenty-four (89 per cent) to 1:100,000, and all twenty-seven to 1:50,000.

### DISCUSSION

Failure to find histamine or a histamine-like substance in the extracts does not, of course, rule out the possibility of the presence of other irritating substances. Data on the chemical analysis of dried molds are meager. Those available fail to reveal known irritative constituents which, under the conditions of extractions employed, could be removed in sufficient concentration as to produce reactions in normally sensitive individuals.

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Protein, according to Cramer<sup>4</sup>, is present in molds in relatively high concentrations (30 to 45 per cent), but its nature is not definitely established. It is known, however, that most fungi contain a variety of different enzymes<sup>10</sup>, some of which are proteolytic; these make possible the presence of peptone and other products of protein hydrolysis which may be irritants. Most of these enzymes, presumably, are inactivated by drying and extraction, but there is no reliable information that this is actually so. One enzyme, histaminase, has been found in a number of molds, including the *aspergillus* group<sup>20</sup>; this enzyme may account for the absence of histamine in the extracts.

Peptone, either in the form of a residuum of the culture-broth or in the form of mold protein, does not itself seem to be the likely irritant in the concentrations in which it exists in the extracts. Although commercial peptone has been reported to produce wheal formation in the human skin in a 1:100 concentration, and contraction of the guinea-pig uterus in a concentration of 1:1,000, such results, according to some workers, are due to contamination with histamine. Hanke and Koessler<sup>11</sup> found as much as 0.003 gm. of histamine dichloride per 100 grams of peptone in some commercial preparations. Using Bacto peptone the writer has failed repeatedly to obtain positive skin reactions with a 1:100 solution and contractions of the guinea-pig intestine with a bath concentration of 1:500.

Besides the better known hydrolytic products of proteins which may be present in the extracts, there may also be toxins of highly complex and unknown chemical composition. Various endotoxins, of course, are found in certain fresh fungi; these are effective in minute amounts. Nothing, apparently, is known about their presence and activity in dried forms subjected to extraction with a higher alcohol. There seems to be a need for fundamental studies of these endotoxins along the lines accomplished by Waksman and his associates<sup>19</sup> for actinomycin A and by Robinson and Moliter<sup>16</sup> for tyrothricin.

In attempting to account for the so-called "irritative" and nonspecific reactions of the extracts in the absence of known toxic substances, it might be emphasized that the skin of normal individuals varies greatly in response to a variety of "stimulants." As a result of trauma by physical or chemical agents there is supposed to be liberated either histamine or a histamine-like substance (H-substance of Lewis) which acts upon the cutaneous vessels to produce the wheal and surrounding flare. Such a reaction can be produced by the injection of a number of chemical agents (such as codeine, morphine, atropine and various ions) and by mechanical means. Injury, whether produced physically or by nonspecific chemical irritants, results in reactions which cannot be differentiated from specific reactions produced by allergens.

In returning to the failure to find histamine-like substances in the mold extracts, it is emphasized that the smooth muscle segments used as

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target tissues responded to histamine concentration of 1:150,000,000; many reacted to 1:300,000,000 and a few to 1:600,000,000. Such concentrations are approximately one thousand times less than the average minimum concentration necessary for wheal formation in the normal human skin. If the mold solutions in question give nonspecific reactions due to the presence of undetectable histamine, individuals so reacting must therefore be 1,000 times more sensitive than the guinea-pig ileum—the most sensitive tissue to histamine yet known. This does not seem likely.

### SUMMARY AND CONCLUSION

It has not been possible to demonstrate the presence of histamine or a histamine-like substance in the washings of *Aspergillus niger* or *Alternaria tenuis*, or in the broth on which these molds have been cultured. Nor has it been possible to detect histamine-like substances in concentrated extracts of these molds employed in skin testing.

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## MOLD FUNGI IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASES

### III. Immunological Studies with Mold Extracts

#### 4. Skin Tests with Broth and Washings from Mold Pellicles

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FOLLOWING the failure of Selle to demonstrate by animal experimentation the existence of histamine-like substances in the broth in which *Alternaria tenuis* and *Aspergillus niger* pellicles had been grown, in the saline washings of these pellicles, or in the allergenic extracts prepared from them, it seemed appropriate to study further the broth and washings by testing them on the human skin. However, inasmuch as no patients were available in whom sensitization to *Aspergillus niger* was considered significant this study was limited to the broth and washings of *Alternaria tenuis*. Nine individuals with a negative history of allergy were tested by the intradermal method with routine *Alternaria* extract 1/1000 and 1/100 and with the twentieth, fifteenth, tenth and fourth saline washings from the pellicles and with the culture broth itself. Eight of these normal controls were likewise tested with varying dilutions of histamine base.

Thirteen patients with respiratory allergy in whom *Alternaria* was considered an important causative factor were likewise tested with the washings and broth. In three of these allergic individuals the testing could not be carried out all the way down to the broth, in one case because the testing produced a systemic reaction and had to be discontinued.

Table I shows the result of testing in the nonallergic series. No significant reactions were obtained with the *Alternaria* extracts or with any of the washings or broth. The eight individuals of the control series tested with histamine gave positive reactions.

Table II shows the results of testing in *Alternaria*-sensitive patients. It is significant that in every instance in which it was tested the broth gave strong reactions. Furthermore, the washings likewise gave definitely positive reactions in nine of the patients, and precipitated asthma in one instance (Case 6).

#### DISCUSSION

In this small series of nine normal individuals, *Alternaria* extracts as well as saline washings from the pellicles and the broth in which the pellicles are grown do not appear to be skin irritants. On the other hand, washing the pellicles in saline solution prior to extraction seems to remove at least a portion of the substances capable of producing positive skin tests on *Alternaria*-sensitive patients. This observation is offered as a possible explanation of the lack of potency in previously prepared extracts.

Presented before the Association of Allergists for Mycological Investigations, St. Louis, Missouri, January 21, 1944.

# RESPIRATORY ALLERGIC DISEASES—PRINCE

TABLE I. RESULTS OF SKIN TESTS IN NINE NONALLERGIC INDIVIDUALS

Case	Alternaria 1/1000	Alternaria 1/100	Washings Alternaria SB-6					HISTAMINE BASE			
			20	15	10	4	Broth	1/1,000,000	1/100,000	1/10,000	1/1000
1 Mrs. T.P.P.	—	—	—	—	—	—	—	—	?	++	+++
2 R.H.	—	—	—	—	—	—	+	—	—	—	+++
3 F.A.H.	—	—	—	—	—	?	+	—	?	++	+++
4 L.T.	—	—	—	—	—	—	—	—	+	++	++
5 E. H.	—	—	—	—	—	—	—	—	+	—	+++
6 W.S.	—	+	—	—	—	—	—	—	+	—	+++
7 Mrs. B.W.	—	—	—	—	—	—	—	—	—	+++	
8 Mrs. M.D.P.	—	—	—	—	—	—	—	—			
9 Mrs. R. E. D.	—	?	—	—	—	—	—	—	?	++	

TABLE II. RESULTS OF SKIN TESTS IN THIRTEEN ALTERNARIA-SENSITIVE PATIENTS

Case	Alternaria 1/1000	Alternaria 1/100	Washings Alternaria SB-6				
			20	15	10	4	Broth
1 H.D.		++	—	?	?	+	+++
2 J.S.	+++	++++	+	+	+	+	+++
3 S.D.	++	++	+	++	++	++	++++
4 S.R.R.	++++	++++	++++	++++			
5 M.S.W.	++	++++	+	+	+	+++	++++
6 S.W.	+++	+++	++	+++	++		
7 E.S.	++	++++	++	+++			
8 J.L.	+	+	++	++	++		
9 S.C.		+++	+	+	+	++	+++
10 C.M.		++++	++	++	+++	++++	++++
11 Mrs. D.S.	+++		+++	+++	+	+++	++++
12 P.W.	++	+++	?	?	+	+	++++
13 D.G.	++	+++	+	+	+	+	++++



## MOLD FUNGI IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASES

### IV. Skin Reactions to Molds as Correlated with Relative Importance in Treatment

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THE data presented herewith have been gathered during three years of testing and treating allergic patients to the air-borne molds. The group includes 705 patients from San Antonio and an approximate radius of fifty to seventy-five miles. All of the patients were tested with a 1-100 dilution of the concentrated mold extracts as prepared by the Association of Allergists for Mycological Investigations, using the intradermal method. *Alternaria*, *Hormodendrum*, *Penicillium*, *Helminthosporium* and *Aspergillus* were used.

The 705 patients are classified according to allergic manifestations as follows:

- 234 (34 per cent) with asthma primarily.
- 396 (56 per cent) with hay fever.
- 18 (2.5 per cent) with sinusitis in which an allergic component was suspected.
- 10 (1.6 per cent) with headache in which an inhalant component was suspected.
- 5 (0.7 per cent) with allergy of the eye.
- 30 (3.8 per cent) with allergy of the skin or cases in which the diagnosis of allergy was not absolutely clear.

The group included all ages from three months to eighty-three years. There were 404 females and 301 males. The numbers and percentages of patients who reacted to and were treated with the various molds may be classified as shown in Tables I and II.

Two hundred and ninety-eight (41.7 per cent) did not react to any of the molds. 163, or 23 per cent, reacted to one mold only. One hundred and one (14.5 per cent) reacted to two molds. Eighty-eight (12.5 per cent) reacted to three molds; forty-six (6.5 per cent) reacted to four of the molds and only eighteen (2.5 per cent) reacted to all five molds.

In correlating treatment with the molds it was found that of the 144 patients treated with *Alternaria*, sixty-eight (40 per cent) were treated only with *Alternaria*, while 60 per cent were treated with *Alternaria* in combination with one or more of the other molds. Of the forty-six patients treated with *Hormodendrum*, nine (20 per cent) were treated only with *Hormodendrum*, with 80 per cent treated in combination with one or more molds in addition to *Hormodendrum*. Of the twenty-six patients treated with *Penicillium*, only four (16 per cent) were treated with *Penicillium* alone. Of the eighty patients treated with *Helminthosporium*, twenty (25 per cent) were treated with *Helminthosporium* alone, leaving sixty (75 per cent) treated in combination with the other molds. Of the

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## RESPIRATORY ALLERGIC DISEASES—ZINK

TABLE I. SKIN REACTIONS TO MOLDS

Molds	Negative		Slight		Moderate		Large	
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
Alternaria	370	52.9	130	17.7	113	16.4	92	13
Hormodendrum	489	69.3	120	17.0	84	11.8	12	1.9
Penicillium	563	79.0	78	11.4	49	7.5	15	2.1
Helminthosporium	454	64.4	98	14.0	87	12.3	66	9.3
Aspergillus	462	66.7	130	17.7	90	12.7	23	2.9

TABLE II. PATIENTS TREATED

Molds	Number	Per Cent
Alternaria	144	20
Hormodendrum	46	6.5
Penicillium	26	3.6
Helminthosporium	80	11.0
Aspergillus	44	6.3

forty-four patients with *Aspergillus*, only five (12 per cent) were treated to that alone, while 88 per cent were treated with *Aspergillus* with the other molds.

On the basis of reactions to skin testing to the molds and other pollen, food and inhalant allergenic factors, and the subsequent clinical course of the patient, it was felt that the molds were probably of no importance clinically in 524 (74.5 per cent) of the patients. It was thought that they were of slight importance in sixty-seven (9.5 per cent) and of appreciable clinical importance in 114 (16 per cent) of the patients. Therefore, it was concluded that the air-borne molds were clinically important in 25.5 per cent of the patients tested and treated.

It might be important to mention that mold counts on vaseline slides exposed over a period of two and a half years have shown that there is no time during the year in San Antonio in which *Alternaria*, *Hormodendrum* and *Helminthosporium* are not present in the air in some quantity. *Alternaria* counts average about thirty spores per day with somewhat higher peaks observed in July and December.

Constitutional reactions to *Alternaria* in the 1-100 and 1-1000 dilutions, *Hormodendrum* 1-100 and 1-1000, and *Helminthosporium* in the 1-100, 1-1,000 and 1-10,000 dilutions have been observed.

### CONCLUSIONS

1. Air-borne molds were thought to be important clinically in 25.5 per cent of the 705 patients tested.
2. *Alternaria* was considered the most important of the molds in treatment, with *Helminthosporium* and *Hormodendrum* less so.
3. *Aspergillus* and *Penicillium* were found to have little clinical significance in the treatment of allergic diseases.

## FOOD ALLERGY

### II. The Technique and Clinical Application of Individual Food Tests

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THIS communication is concerned with the presentation of the clinical use of individual food tests, in conjunction with skin tests, in the diagnosis of food allergy. It is based upon information gleaned in a large series of tests performed by the technique reported herewith, over a period of ten years with essentially the same method. Much of the information was obtained by making twenty-four hour observations on an original patient for six consecutive months and two subsequent patients, one of whom was kept under such study for six weeks, while the third was observed in like manner for four months. I should like to emphasize that more was learned, concerning the use and value of food tests, from these three controlled patients than from all the other studies.

There is need for a correlated exposition of diagnostic measures other than skin tests since none of the textbooks on allergy, at this time, present such detailed procedures co-ordinated for clinical application.

#### I. PREREQUISITES FOR THE USE OF INDIVIDUAL FOOD TESTS

The first, and an absolute, prerequisite for the application of the procedures outlined herewith, other than skin testing, is that the patient, if his symptoms are not wholly due to foods, is fully protected against all inhalant factors. While this statement implies a considerable amount of detailed work which cannot be discussed in this paper, it should be mentioned that this infers the patient's degree of sensitivity will have been determined and that the treatment dose has been governed by the degree of sensitization for each of the specific inhalants. The necessity for protection against inhalants is not based upon any presupposition that all symptoms not controlled by inhalants are necessarily due to foods, but to prevent error, in the individual food tests, in those patients sensitive to inhalants (possible contact during test).

The second requirement for the use of these diagnostic measures is that the physician be thoroughly acquainted, both didactically and clinically, with the nature and dynamic mechanism of food allergy.<sup>9</sup> This means that the physician should perform these tests himself until he is entirely acquainted with all these factors.

A third and important fact to keep in mind is that, with present technique of testing, there is no single method, or combination of methods, of testing a food on one occasion, which will yield information that becomes a permanent guide as to the exact subsequent use of that food by the patient.

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### II. THE TECHNIQUE OF INDIVIDUAL FOOD TESTS

The method of testing foods individually, as described in this article, was originated in October, 1932, and by October, 1934, the technique was standardized and has remained practically constant since that time. While more than 25,000 tests have been made by this method, only the exceptions to the rule were discovered after the first 500 were performed.

*Preparations Preliminary to the Test Day*.—The food to be tested should be used regularly in the diet for at least two weeks preceding preparations for the test. It should then be avoided exactly four days and tested on the fifth day.

*Preparations of the Food Used for Tests*.—The food must be prepared individually without added condiments, sugars, et cetera, using an average portion which is to be eaten within five minutes' time. Should the food fail to produce definite symptoms, at the end of one hour repeat the feeding, using one-half portion.

*Instructions for Patient on the Test Day*.—The patients are instructed to take neither food nor drink for five hours preceding the feeding time. They are to avoid all medicine for four hours and drinking water and smoking for three hours immediately preceding the start of the test. Be sure to ascertain, before starting the test, if these instructions have been carried out.

*The Objective and Subjective Studies of the Tests*.—The following are the objective and subjective studies which are made as part of the individual food test. These observations are made for one-half hour before the test, for one hour after the first feeding, and for one-half hour after the second eating of the food. The patient must be kept in a constant environmental status, i.e., avoiding exercise, argument, drafts and change in posture.

1. Observe the patient for:

- (a) Nasal symptoms: sneezing, watering, itching and blockage
- (b) Chest symptoms: clearing of the throat, coughing, wheezing
- (c) Inquire concerning the occurrence of tiredness, headache, pain of any description, pruritus of the skin, lips, palate, throat, et cetera, hives, gastro-intestinal symptoms, such as nausea, bloating, cramps, retasting, et cetera. Pay particular attention to the occurrence of a "chilling sensation." It may be overlooked if one is not aware of its occurrence. Observe for perspiration, without other adequate cause.

(d) Make delayed observations of a comparative nature, i.e.: compare symptoms during the night after the test and the following morning, with the condition existing the night and morning just before the test. In order to make observation "d" of any value, it is imperative that a patient not use any food the day of the test except the test food, unless it was eaten the day previous.

## 2. Record the following:

(a) The pulse and respiration rate, as well as the blood pressure, at the end of the thirty-minute rest period before eating. Also take these readings at twenty, forty and sixty minutes after ingestion of the food, with a final reading at the end of the test, that is, thirty minutes after the second feeding.

(b) Take leukocyte counts at the end of the thirty-minute rest period, then again at twenty, forty and sixty minutes after the initial ingestion of the food.

(c) Make total eosinophile counts at the same time that the white blood counts are taken.

(d) In the thermal types of food allergy, subject the patient to chilling following the test. All these procedures are to be carried out in the office, under the direct observation of the physician.

Originally, when I began the individual food tests in October, 1932, only the preparations for the test and the first three steps were carried out.

In 1933 (when Vaughan<sup>11</sup> described the leukopenic index, blood counts were added to the studies. It was found that the criteria of blood count changes for sensitization as advocated by Vaughan's first paper, did not entirely coincide with the clinical findings and the counts were discontinued temporarily. In October, 1934, the leukocyte counts were added again to the studies when it was observed that a trajectory type of curve, with postprandial counts, made at twenty, forty and sixty-minute intervals, coincided with compatible foods. These observations were made in a patient with extreme asthma who was observed twenty-four hours daily, for six weeks. There was no possibility for error in ingestion nor did any symptoms occur which were unknown to me. The patient was not only freed of symptoms when the diet was limited to the foods giving this type of curve, but has continued to remain free of symptoms for ten years except for deliberate dietary tests or accidental ingestion of foods. It seems reasonably safe to assume that this curve indicates a food that is nonallergic. Furthermore, this possibility has been studied in many subsequent instances, and it yet remains to be proven that a food, properly tested, which gives a trajectory type of leukocyte curve, *is not compatible under conditions of the test*. The hypothesis that definite leukopenia is evidence of food disagreement has been found to be much more valuable than the contention that if a food did not produce a drop of at least 1,000 cells, it was not a cause of symptoms. Gay<sup>5</sup>, in a paper on peptic ulcer, indicated that foods which produced a drop of only 300 cells would sometimes be a cause of allergy. Editorially, the American Medical Association<sup>3</sup> criticized this, stating that blood cells could not be counted within an accuracy of 300 cells in successive counts, missing entirely the obvious implication of Gay's statement. Gay was well acquainted with the limitations of accuracy of counting blood: he was calling attention to the fact that foods which did not alter the count by as much as 1,000 cells were ac-

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tually the cause of symptoms, and one could not assume that when the leukocyte count did not drop 1,000 cells, that the food was compatible.

At the present time the value of the leukocyte counts lies in the finding of (1) compatible curves<sup>10</sup> and (2) in the finding of marked leukopenia without the association of symptoms. In these latter cases, one is to be on the alert for two facts: (1) the occurrence of delayed reactions, ten to fourteen hours after eating and (2) the probability of cumulative reactions (Phase III).<sup>9</sup> This will be discussed, under clinical application of tests. Wide fluctuations of the counts are highly suggestive of food disagreement.

The final additions to the food test were the inclusion of the pulse rate<sup>2</sup>, as a routine measure in 1942, and the total eosinophile count, using Randolph's<sup>7</sup> technique in the past year.

The study of thermal factors was started in the fall of 1937.<sup>4</sup> This is best done by exposure to air below the critical temperature for a patient or by approximating chilling by means of ice, or immersion of the hands in ice-cold water. Thus, except for the total eosinophile counts, and the routine study of the pulse rate, there has been no change in the technique of the test during the past seven years.

There are a number of points which should be stressed concerning the clinical use of these tests:

First, if a patient cannot be freed of symptoms after making individual tests of the ten to twelve most common articles in the diet, there is no real cause to believe that the performing of sixty to one hundred tests will relieve the patient.

Second, clinical advice to the patient must be made in terms of the previous use of the food and the type of food sensitization involved. For example, if a food is found compatible on testing, it must be subsequently determined whether this is a perennial, a co-seasonal or a thermal type of food allergy. If the food has been eaten three times weekly before testing, the patient is to be advised to continue using it with this frequency. The patient may develop an allergy to this food if the incidence of ingestion is increased (Phase III).<sup>9</sup> If the test is made in July, the patient cannot be assured as to the effect of the food during the ragweed season or during the winter months as concomitant inhalant factors occur in pollen seasons and thermal effects in winter.

Third, food tests, properly performed and interpreted, will be diagnostically accurate in approximately 90 per cent of the tests. It should be emphasized that the selection of cases, i.e., perennial nasal allergy, asthma or migraine, et cetera, will determine, to a great extent, this average accuracy. The figures given here are made up chiefly from patients with perennial nasal allergy, asthma and seasonal hay fever, with a small per cent of migraine, eczema, hives and gastro-intestinal allergy.

Fourth, patients improve with the elimination of foods whose sensitization can be proved by this type of test. The greatest value of individual

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food testing is the clinical observation of the effects produced by a food in the test period. This study has been neglected apparently by most students of the individual food test methods. It is absurd to have a patient in the office for two and a half hours for blood counts, and to attempt to make a diagnosis by use of these alone, when this same period of time may be used for the purpose of clinical observations if the patient has been properly prepared. During the first two years, the test procedure consisted of clinical observations alone, blood counts being added in 1934.

### INTERPRETATION OF CLINICAL FINDINGS

*Symptoms of Sneezing, Watering of the Nose and Coughing.*—These are recorded as they occur for one-half hour before eating and for the duration of the test. Patients are advised not to blow their noses until the secretions are profuse enough that the nose will drip. This is considered a unit, i. e.: one watering of the nose. Patients should avoid "sniffing," but if they do so, or in the young, this may be taken as a unit, but must be used as such throughout the whole test. Sneezing is recorded as it occurs. Both coughing and clearing are registered under coughing. Itching of the nose, or any other type of oral pruritus is elicited at the start of the test, its presence or absence noted and the patient instructed to report its occurrence, as soon as symptoms occur. The patient is questioned for these at the time of each leukocyte count. Nasal blockage is likewise registered and studied throughout the test.

The value of these studies will be in terms of the acuity of the observer, correctness of preparation for the test and, in some instances, the co-operation of the patient. It has been found that some patients knowing that excessive nasal symptoms indicates disagreement of a food, will attempt to subdue their reactions. Children reacting to a food they like often attempt to hold down the normal tendency to cough. The findings are considered significant if the food produces a doubling of the incidence of symptoms. Many times the food causes allergy and will not double incidence; however, this is a conservative rule.

If one uses the incidence of symptoms only as a means of diagnosis, more foods will be eliminated at the start of the study than need to be kept out to relieve the patient. When eliminations are made upon this basis, a recheck should be made as soon as definite clinical improvement occurs, or upon freeing the patient of all symptoms. The clinical value of this test increases as the patient improves. If a person is entirely free of all symptoms before eating, the definite occurrence of sustained symptoms is highly significant.

Among patients who develop post-ingestive symptoms during the first hour, the highest per cent commence to have symptoms ten minutes after eating, the next highest per cent at five minutes, and the remainder will occur throughout the hour, being progressively less, with the increase of time after eating. These studies are among the most valuable of all food allergy diagnostic methods available. They have proved valuable when all

other means have not been of help. They will only be ineffective if one disregards the factors that influence their occurrence.

*Symptoms of Tiredness, Pain, Pruritus of Skin, Headaches, Gastro-Intestinal Symptoms of all Types.*—These are determined before, during and at the completion of the test. Tiredness is probably one of the most significant symptoms, usually developing within forty-five minutes and often fleeting.

*Blood Pressure, Respiration and Pulse Readings.*—Blood pressure readings have been made only in patients subject to increased pressure. Some of these cases have been studied for seven years in whom there was a constant demonstrable relation between specific articles in the diet and post-ingestive hypertension.

Respiration will usually increase in rate at the beginning of the bronchial reaction. Since increases in the respiratory rate are seldom seen, without other more significant symptoms, this observation is only confirmatory. Pulse readings have been made from time to time, but have been routine for the past two years, chiefly in an attempt to evaluate their use. At this time it may be stated there are (1) patients who have no other test period findings of reaction than an increase of the pulse rate, and (2) there are many food allergies not associated with changes in the pulse rate, (3) that post-ingestive tachycardia is not the rule with agreeable foods and (4) that the most valuable feature of the pulse increase is to suggest the occurrence of delayed reactions ten to fourteen hours after the test. Thus, this feature is, along with marked leukopenia without any symptoms, the signs for alertness in observing patients as to delayed effects from the food being tested. This should always be done, of course, when neither of these findings is present.

*Leukocyte Counts.\**—These are made with the same pipette for the same patient, the pipettes are shaken in a mechanical shaker and eight large squares are counted on the same chamber each time. Persons making counts should check their technique by using two pipettes and graphing their results. These must be consistent within the allowed error (5 per cent), in counting and a cross test with another technician should also be made to eliminate the possible identical error one would make with both counts. There has been no change in leukocyte counts since that described in my most recent article on the subject.<sup>8</sup>

The use of leukocyte counts has been subject to criticism<sup>1,6</sup>. That one could seriously and consistently use this test, ignoring the clinical possibilities that obtain at the time of the test, seems unbelievable, but this is the only possible conjecture from these reports. There are only two directly usable features of the leukocyte counts alone, namely: (1) the finding of the trajectory curves, which may be taken to indicate a compatible

\*Clinical findings are recorded on a special chart which is included in the author's reprints.



food, for purposes of clinical application, and (2) the finding of definite leukopenia without any other evidence of disagreement. In this latter case the suggestion is that the patient is apt to have delayed symptoms. Total eosinophile counts, using Randolph's<sup>7</sup> method, have not been used sufficiently long to give us definite interpretive information.

*Thermal Tests.*—It is obvious that since patients with this type of allergy<sup>4</sup>, will have only their major symptoms during cold weather, it will be quite easy, as a rule, to subject the patient to normal exposure to cold air. If this is not possible, then simulate with ice or ice-cold water the chilling effect and observe the patient thereafter for one-half hour or an hour, depending upon the circumstances.

The occurrence of "chilling sensation" following the eating of foods occurs in many patients who are not major cases of thermal allergy. This symptom may be elicited the same as tiredness.

#### CRITERIA FOR THE SELECTION OF FOODS TO BE TESTED

If a patient, after he has been adequately tested and treated for inhalant allergies (this would not be true in migraines and gastro-intestinal patients as a rule), presents a chain of symptoms which are either typical of food allergy or could in all likelihood be due to foods, then certain articles in this patient's diet are selected for tests. This selection is based upon probability.

Probability has been determined by the analysis of several hundred patients in whom symptoms did not recur except with deliberate ingestion. It was found that wheat, egg, milk, corn, oranges, tomatoes, string beans, Irish potatoes, et cetera, was the numerical order of frequency of foods causing symptoms. Therefore, a patient who failed to react upon skin testing, or who failed to be relieved of his symptoms when placed upon a diet based upon positive skin tests for foods, in conjunction with specific and correct inhalant therapy, wheat should be tested first. On the basis of probability, it is the most likely food to be a cause of symptoms. In the selection of foods for individual testing, one must bear in mind that a patient usually consults him for a masked food sensitization. For example, if a patient knows that every time he eats onions he is sick three to five days, he will stop using onions. He comes to you for help because he has symptoms like these created from eating onions but whose occurrence does not seem to bear any relation to a given food, or else he thinks he is sensitive to all foods. This is a typical story of a patient with masked food allergy. For this reason, no matter how thorough a history may be, it cannot be used to diagnose the specific food allergy as some advocate.

The selection of foods for testing will be discussed for each disease in particular, in order to detail minor syndrome characteristics.

1. *Asthma.*—The following are the clinical characteristics of existing food allergy in a patient properly treated for inhalant sensitizations:

(a) The production of large quantities of mucus. While inhalants may produce copious quantities of mucus this will not be true for the inhalant treated individual unless he contacts a rare inhalant and then the history of the attack should be diagnostic (flour mill dust, et cetera).

(b) The occurrence of acute attacks lasting from two to five days, the latter only in association with purulent secretions, when there have been no essential changes in environmental contacts.

(c) In patients who live in the same house, sleep in the same bed and work at the same job, acute attacks commencing in the middle of one night of the week are so typical of food that they are considered, for the purpose of clinical procedure, as being due to foods until disproved.

(d) Either of the attacks as described under "b" and "c" may be superimposed upon another characteristic pattern of food allergy, namely, the patient who has difficulty, in spite of treatment, from the time he first awakens until an hour or two after breakfast, or even as late as 11:00 a.m. and then feels quite well the remainder of the day.

(e) The most typical, but not necessarily the most common, is the occurrence of asthma every afternoon about 4:00 to 5:30, not related to, or affected by, other inhalant or environmental factors. This is typical of a food eaten at breakfast and repeated at luncheon.

2. *Perennial Nasal Allergy*.—The five clinical syndromes described with asthma, occur in nasal allergy, except that the symptoms are nasal instead of bronchial and are in the treated individual indicative of foods until disproved. In addition to these, the continuation of nasal occlusion in a treated patient, must be taken as a sign of food complications again, until disproved. One will often see patients with this syndrome in whom there are either no, or very few, inhalant sensitizations, and in whom all skin tests for foods are negative. These patients are primarily problems of food sensitization. In connection with this statement I would like to emphasize, however, that in sixteen years of allergic practice I have found only two patients in whom all symptoms of respiratory allergy could be controlled by diet alone. In all the others, there was a mixture of sensitizations of foods and inhalants.

3. *Migraine*.—The selection of foods for testing in patients with migraine, is determined by the type of clinical symptom pattern. In the first the patient would have intermittent paroxysms of typical symptoms, two to three days in duration, spaced at various intervals. Between these attacks he is entirely free of symptoms, which implies absolutely no pruritus of the nose, roof of mouth, nor any tiredness nor tachycardia. The second type of patient is the one who is never free of headache, pruritus and tiredness. This person has superimposed on his constant level of symptoms acute exacerbations lasting two to three days. In the first instance, the diagnosis can certainly be suggested by the diet record alone, but it must be substantiated by the individual test. The diagnosis of the specific

effect of a food is never made by improvement following its elimination. It must always be made upon the basis of the effect produced by the proper reintroduction of the food to the diet (food test). In the second group of patients we are dealing with foods used constantly as well as those used intermittently. In the study of migraine one must consider tiredness as the predecessor of headache. A food which is taken every three or four days and produces only tiredness will, if used repeatedly, produce headache.

If the skin tests have not been successful in detecting the cause of a constant pattern of symptoms, then individual tests are to be made, based again on probability. Therefore, it is imperative that early in the diagnosis of these cases that adequate diet records are kept although most patients will not deviate greatly from the common probable causes, but there may be exceptions, as, for instance, a patient extremely fond of asparagus, or a patient who always insists on eating avocados, or who constantly uses prunes. Exacerbations in migraine patients can be due to two things: either the increased use of one food or the occasional use of a specific food. For example: a patient may eat peanuts once every third day and will be subject to more or less constant tiredness, but if they are used three or four meals in succession, will have a very definite headache. These two conditions will only be revealed by a diet record. Headaches due to foods may occur during catamenia only.

4. *Eczema and Hives*.—The selection of foods for testing in these patients is not greatly different than the other allergic diseases except that in urticaria the duration of food symptoms may be much longer than in either asthma or hay fever. In the case of eczema, pruritus (not pathologic changes in the skin) is to be used in the determination of offending foods. Thus, a patient with food eczema continues to suffer from pruritus only as long as he continues to ingest products to which he is sensitive. Pruritus usually subsides in fifty to seventy-two hours after the last eating of the food to which the patient is sensitive, but the eruption may not clear up for as much as twenty days afterward. In the patient with eczema, pruritus when due to a food used constantly will show exacerbations late in the morning but, more typically, late every afternoon as well as in the middle of every night. This is all evidence of a food used constantly in the diet.

5. *Gastro-Intestinal Allergy*.—The selection in these patients needs little emphasis except for two points.

(a) In a patient who has a probable gastro-intestinal allergy, one should bear in mind that sensitization is only one of many probable causes of such gastro-intestinal symptoms and, therefore, a complete differential diagnostic study is imperative.

(b) With patients treated for ulcer who have not responded to the treatment, the food used constantly in the treatment of ulcer assumes more

## FOOD ALLERGY—RINKEL

importance as a likely cause of trouble and probability would differ, therefore, from the general rule. In other words, milk, instead of being the third most likely food to cause symptoms, would be the most likely; then egg, cereals, et cetera.

### CLINICAL APPLICATION OF THE TEST

The test should be performed with due regard to the nature and the dynamic mechanism of food sensitization. This means that one must create by immediate avoidance of the food, the condition for maximum clinical response, for it is the clinical evidence (symptoms) that constitutes the greatest value of the test. Further, the food must not be out of the diet long enough for the patient to gain partial tolerance (Phase II).<sup>9</sup> Patients who gain tolerance, that is, pass through Phase II of the cyclic changes within a short time, may give an asymptomatic response to the food if the test is made after elimination of the food for longer periods of time. Whenever a patient is tested and is found not sensitive to a food, the use of the food in the future must be in terms of the immediate past. For example, if one tests a food that is used but once in ten days, and it is found to be compatible, you can advise its use only once every ten days in the future, with assurance that under the conditions of the test (co-seasonal or thermal), the food will remain compatible. Therefore, it is not very wise to check foods individually unless they normally are used almost daily. It is necessary to recheck a food, if one wishes to change its use from once bi-weekly to daily. One cannot assume by means of any test method, that it will remain agreeable for the patient, if the frequency of the ingestion is increased. It is also imperative to know that a food, tested and found to be compatible, may be added to the diet and used for two or three weeks and then the patient will have an insidious onset of symptoms which will not be immediately related to the ingestion of this food. Yet this food is the cause of the patient's distress. Thus, one must be on the alert for Phase III<sup>9</sup>, of the cyclic changes, when changes in the dietary incidence of a food are advised. This change is most likely to occur with foods previously known to be a cause of allergy, which have been omitted for months and are readmitted to the diet following rechecking. It is possible for these foods to recreate an allergic status even when used but once every third day and completely mask their ill effect when used at that interval. If foods are tested in a patient who has a history of thermal factors, then they should be rechecked when it is possible to evaluate the thermal factor. It is possible, but not nearly as desirable, to simulate the thermal exposures. Patients who are subject to seasonal air-borne products cannot be advised by tests, run out of season, as to the effect of these foods during exposure to specific seasonal inhalants.

Since there is no perfect individual food test, it becomes obvious that such testing to be of value to the physician and in turn, to the patient, must be a part of a systematic, concise approach to the clinical problem of food allergy. Therefore, these tests will serve best when there is a correlated

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application of these various procedures, together with the treatment of other etiologic agents.

The keystone of the diagnosis of food allergy is to have a patient symptom-free, upon a known diet, for a consecutive period of a week or ten days. To the attainment of this, all tests and diagnostic procedures should be co-ordinated. When this has been accomplished one will be able to complete the studies without using additional individual tests.

A brief outline of such method is the following:

First is the use of skin tests, followed by the avoidance of such foods to which the patient has given reactions. If this elimination and the concomitant therapy of inhalants has failed to relieve the patient in whom food allergy could be a factor, further studies are carried out. The need for these tests will be greatly enhanced if the symptoms, observed after the patient has been under treatment, have the characteristic nature and time of reaction frequently seen with foods. When these two facts are considered of sufficient import to warrant the use of individual testing, such tests are to be performed. If the patient is one who has a high degree of inherent tolerance<sup>9</sup>, the restricted diet of foods found agreeable are to be used for a period of a week, as a test diagnostic diet. This will be possible more often than not.

In the patient with a low inherent tolerance<sup>9</sup>, it is best not to prescribe a restricted diet of a few foods but to employ a diversified rotating diet, checking possible allergies when diet and symptoms records indicate these possibilities.

It is of extreme importance to differentiate first between failure to obtain relief of allergic symptoms due to our inability to make a correct diagnosis and, secondly, from our failure to obtain relief because the patient does not know where foods are contacted. Finally, one must differentiate diagnostic error from therapeutic failures due to non-co-operation of the patient. The end results of the use of any diagnostic procedures in allergy, are not entirely due to the perfection with which the physician applies the method, but are as much, if not more, dependent upon the thoroughness with which a patient adheres to the findings obtained by such test procedures.

### SUMMARY

1. The technique of individual food tests has been outlined.
2. It is suggested that this test be employed to confirm all skin reactions.
3. The test should be used to discover the specific effects of various foods before assuring they are compatible.
4. The test is to be used in keeping with the basic nature of food allergy as regards incidence and type of sensitization as well as concomitant or thermal factors.

*(Bibliography on Page 517)*

## THE INFLUENCE OF HYPNOSIS ON PASSIVE TRANSFER AND SKIN TESTS

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THE psychogenic factor in allergy is receiving increasing attention in recent years. Among the various aspects of the psychogenic viewpoint the work of Clarkson<sup>1</sup> on hypnosis has been cited in the recent textbooks of Feinberg<sup>2</sup> and Vaughan<sup>4</sup> and in an article by Peters<sup>5</sup>. Clarkson reported the following case:

"On preliminary investigation an asthmatic girl, aged eighteen, gave a severe cutaneous reaction to an intradermal test for egg sensitization. A wheal one inch in diameter surrounded by a raised erythematous zone three and a half inches across developed around the site of inoculation. Next day the test was repeated whilst the patient was deeply hypnotized. The suggestion was given that no reaction would occur. The patient was kept under hypnosis for half an hour and the suggestion frequently repeated. No wheal developed and there was no erythematous blush. Sphygmographic tracings of the pulse were taken before and during the experiment. As soon as hypnosis was induced the tracing altered markedly. The excursions became accentuated and more frequent. There was a sharp rise and fall. The pre-dicrotic notch was registered close to the base line. The blood pressure increased from 110 mm. Hg systolic and 65 mm. diastolic to 130 mm. Hg systolic and 75 mm. diastolic. Next the experiment was repeated in the patient's normal state and the original wheal was obtained."

As Clarkson reported only this one case in which hypnosis and suggestion seemed to influence the skin response, and as there is no reference in the literature corroborating such an effect, it was decided to repeat the experiment under various conditions.

### METHOD AND RESULTS

Two patients, one with bronchial asthma and one without any allergy neither of whom reacted to skin tests with ingestants or inhalants, were passively sensitized by the intradermal injection into both forearms of 0.1 c.c. of Wassermann-negative serum from a patient known to be sensitive to ragweed. Twenty-four hours later one of the sensitized areas was injected with .01 c.c. of a 1:500 dilution of ragweed extract. A four-plus wheal with erythema resulted in fifteen minutes. Control areas did not react. On the second day, with the patients under deep hypnosis, a sensitized area was injected with .01 c.c. of a 1:500 ragweed extract and repeated suggestion was made that skin response would not occur. Within fifteen minutes, both patients developed a four-plus wheal with erythema identical with the wheal which appeared the pre-

From the Department of Internal Medicine, University of Illinois.  
Read before the Chicago Society for Allergy, October 16, 1944.

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vious day without hypnosis. The results of rechecks were the same, as were those of a third injection of ragweed extract given an hour after termination of the hypnosis and those obtained when the entire procedure was carried out again. In one of the patients repeated suggestion under hypnosis that non-sensitized areas would react upon injection of ragweed extract failed to produce positive skin tests.

Two patients, one with ragweed hay fever and one with bronchial asthma, presented four-plus skin tests to ragweed extract applied by the scratch method. Both were placed under deep hypnosis during which ragweed extract was again applied by the scratch method and the suggestion repeatedly made that skin response would not occur. Within a few minutes erythema and wheal formation developed as before hypnosis. Application of the extract one hour after hypnosis produced a similar response in the same length of time.

A patient sensitive to cat and dog dander presented wheals one inch in diameter upon application of these danders by the scratch method. Under deep hypnosis repeated suggestion was made that the application of cat and dog dander to the skin scratch would fail to elicit swelling and redness. However, the response developed in ten minutes, just as before hypnosis. On the following day a third application without hypnosis again resulted in the wheal formation described. The same result was obtained a second and a third time.

### COMMENT

In view of the increasing prominence of the psychogenic aspects of allergy, particularly asthma, it would seem highly important to substantiate this phase on as tangible a basis as possible. Certainly, any procedure that would demonstrate an alteration, abolition, or retardation of the allergic skin mechanism would constitute a definite step in this direction. Furthermore, it would offer clear-cut evidence that psychogenic factors act not merely as a trigger mechanism but influence the mechanism itself. For these reasons the case report of Clarkson would assume considerable importance in opening new avenues of study of the allergic reaction if the findings could be corroborated. Apparently some authors have accepted Clarkson's conclusions on the basis of one case report. We have been unable to demonstrate any influence of suggestion in the hypnotic state on atopic skin sensitivity or skin sensitivity produced by the passive transfer method.

### SUMMARY

1. Five patients were studied to determine whether skin responses can be influenced by hypnotic suggestion.
2. Hypnotic suggestion failed to affect the usual response of passively-sensitized skin areas.
3. Hypnotic suggestion failed to affect the skin of patients sensitive to ragweed or to animal dander.

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4. According to these results, hypnotic and post-hypnotic suggestion does not influence skin responses.

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FINDING TUBERCULOSIS. *Bull. Lederle Lab.*, 11:19, (Nov.) 1943.

Tuberculosis is a communicable disease which can be prevented, arrested and cured. Diagnostic tests include X-ray, the Mantoux test and the patch test. The Mantoux test will miss few cases of significant infection when used in strengths of 0.1 mg. O. T. or P. P. D. 1 (first strength). In higher strengths, reactions are probably nonspecific. The patch test, as to dosage and test material, is not as well standardized as the Mantoux test. Both tests are good screening procedures for mass case-work. Three methods given for finding cases of tuberculosis are: through the private physician, through clinical services, and through mass examinations or surveys. The use of skin testing, particularly in the latter group, is important. Because of the simplicity of the application, ease with which positive reaction can be read and the effectiveness of selection, the patch test should be used to discover unrecognized tuberculosis.

L. J. H.

## Food Allergy

(Continued from Page 514)

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# Editorial

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## MAYO CLINIC FELLOWSHIP

The ANNALS is pleased to announce that the Medical Graduate Committee of the Mayo Foundation has approved the placing of a fellowship of the American College of Allergists at the Mayo Clinic and Mayo Foundation. The selection of the person to receive the fellowship will be made by Dr. Charles F. Code, Professor of Clinical Physiology, and the Medical Graduate Committee of the Mayo Graduate School; research work on problems of allergy to be under the direction of Doctor Code in the Mayo Clinic and Mayo Foundation. The stipend for this fellowship will be \$1,500 per annum, with provision for a continuation of the fellowship for a second year, if desirable.

The granting of such a fellowship is necessarily postponed until or towards the end of the war, for the reason that Doctor Code at present is engaged full time in war research, and it would be impossible for him to devote sufficient time to satisfactory researches in allergy. Furthermore, it would be difficult at this time to select a highly suitable man for such a position.

Under similar circumstances, the granting of the fellowship to the Standardization Committee of the College,\* to be directed by Dr. George E. Rockwell of Cincinnati, may have to be postponed for lack of a suitable candidate. The work of this committee and that of the Laboratory Committee is necessarily delayed, although thorough plans are now being made which will greatly accelerate the work as soon as a qualified person is available and the activities of all can be redirected into fields of allergy research.

F.W.W.

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## THE ST. LOUIS GRADUATE INSTRUCTIONAL COURSE

The five-day intensive Graduate Instructional Course, held at St. Louis, November 4 to 8, inclusive, by the American College of Allergists was attended by seventy-two registrants, including twelve officers in the Service, from all parts of the United States. The majority of the registrants were diplomates in their various specialties who desire to apply allergy to their practice and have already applied for Associate Fellowship in the College. There are many whose attention was not attracted to the advertisements and news items concerning this course, which appeared in the various national medical journals. As a result, a number who would have liked to register for the course did not do so. Numerous communications have been received at headquarters to this effect.

The course preceded the meeting of the American Academy of Pediatrics and that of the Southern Medical Association. There were day and

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\*See *Annals of Allergy*, page 438, September-October, 1944.

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evening classes, interspersed by informal discussions, exhibits and practical demonstrations. All registrants were furnished with a set of comprehensive outlines of the lectures, printed on sheets to fit a standard ring book, as well as a mimeographed Manual entitled "Allergy Laboratory and Diagnostic Procedures." Revisions and additions are being made to this Manual, which will be printed and will be available to anyone desiring it.

The instructors for this course, together with the titles of their lectures, appear on page 522 of this issue.

The College is very grateful to the instructors for their untiring efforts and to all those who helped to make the course a success.

F.W.W.

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### THE INDEX NUMBER—AN APPRECIATION

The index, in this issue, to the contents of the literature published in the ANNALS OF ALLERGY for the past year, deserves particular attention. A perusal will reveal the remarkable scope of investigative and clinical allergy and immunology achieved comparatively recently and since the second world war began. The apprehension of the staff, that owing to the diversion of many scientists in foreign fields there would result a paucity of excellent material, has been unnecessary. Besides the outstanding original contributions listed, the comprehensive reviews of the literature on the various allergic diseases initiated by the ANNALS have attracted much favorable attention. The ANNALS brings to the attention of its readers the gist of the pertinent literature without the necessity of pursuing a maze of bibliography, although the references have been very complete for each review article. Readers are urged to refer carefully to this index before looking elsewhere for any subject pertaining to allergy and clinical immunology.

A feature commencing with this issue is the section of abstracts in Spanish which replace the summaries of the original articles. This feature has been added in response to a request by our Spanish-speaking members. It appears as a Supplement to each issue and will be supplied to subscribers upon request.

The staff takes this opportunity to express its sincere gratitude to the numerous members and friends of the College for their invaluable contributions the past year. We invite your further confidence by asking you to continue this vital interest, and sincerely extend to all the Season's Greetings.

THE SECRETARY

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### THE SEVENTH ANNUAL FORUM ON ALLERGY

The Seventh Annual Forum on Allergy will be held in the Hotel William Penn, Pittsburgh, Pennsylvania, on Saturday and Sunday, January 20-21, 1945. This is a meeting to which all reputable physicians are most welcome, and where they are offered an opportunity to bring themselves up to date in this rapidly advancing branch of medicine by two days of intensive postgraduate instruction. For in-

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stance, the twelve study groups, any two of which are open to him, are so divided that those dealing with ophthalmology and otolaryngology, pediatrics, internal medicine, dermatology and allergy, run consecutively. In addition, the study groups are arranged on the basis of previous registration. In this way, as soon as the registrations are completed, the registrant is expected to write the group leader and tell him just what questions he wants brought up in the discussion. Attention is also called to the fact that during these two days almost every type of instructional method is employed. Special lectures by outstanding authorities, study groups, pictures, demonstrations, symposia and panel discussions.

On Friday evening preceding the Forum, the American Association of Allergists for Mycological Investigation will hold its annual meeting at which time the results of their co-operative research on the Allergy to Fungi will be reviewed. All reputable physicians and scientists are invited to attend this interesting summarization of a year of brilliant co-operative research.

Although the program is most intensive, informality and an emphasis on the practical marks the conduct of the whole meeting. Good fellowship at luncheon, dinner and smoker reigns throughout the two days. Last year, the tradition was established of dining together throughout the meeting, thus offering an exceptionally fine opportunity to meet and come to know many distinguished authorities in this new and rapidly advancing field of medicine.

This international postgraduate Society was founded in 1938 at Cincinnati, Ohio, to provide a place in which to review the progress of clinical allergy, to provide in peace times a Forum for the younger members, and to offer intensive postgraduate instruction in allergy to physicians working in other fields. The founders were Dr. Tell Nelson, Chicago, Illinois; Dr. Karl D. Figley, Toledo, Ohio, and Dr. Jonathan Forman, Columbus, Ohio. Annual meetings have been held each year since; in Toledo, Ohio, in 1939; in Chicago, Illinois, in 1940; in Indianapolis, Indiana, in 1941; in Detroit, Michigan, in 1942; in Cleveland, Ohio, in 1943, and in St. Louis, Missouri, in 1944.

In 1940 the name was changed to correspond to the international character of its attendance and the Forum's Gold Medal and annual oration were established as a means of recognizing outstanding contributions to clinical allergy. The first recipient was Bela Schick, New York City, who introduced the word "allergy"; the second was W. W. Duke, Kansas City; the third, Arthur F. Coca, New York City; the fourth, Robert A. Cooke, also of New York City. This year the Forum medal goes to Milton J. Rosenau, Chapel Hill, North Carolina.

This year the Marcelle prize has been established through the generosity of the Marcelle Cosmetics, Inc., and will be given to the author of the best papers on Allergy appearing in the American medical literature during the year. The first prize will be for three hundred and fifty dollars and the second prize for one hundred and fifty dollars. The awards will be based on the decision of a jury of distinguished allergists.

For further information, copies of the book and registration, write Jonathan Forman, M.D., Director, 956 Bryden Road, Columbus 5, Ohio.

# News Items

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Dr. F. W. Wittich has been elected an active member of the American Association of Immunologists.

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Please make your transportation and hotel reservations now for the Forum meeting to be held at the Hotel William Penn, Pittsburgh, January 20 and 21.

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Dr. J. Warrick Thomas, Richmond, Virginia, has accepted a position on the Editorial Council of the *American Journal of Digestive Diseases* at the invitation of Dr. Beaumont S. Cornell, Editor.

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Colonel Sanford W. French (MC Ret.) announces the opening of offices at 218 Encino Avenue, Alamo Heights, San Antonio 2, Texas. His practice is limited to the diagnosis and treatment of allergic diseases.

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As formerly, all Fellows of the College who are in the Armed Forces have been furnished by Marcelle Cosmetics, Inc., complimentary, a complete set of the printed abstracts of the courses presented at St. Louis. Numerous expressions of appreciation have been received for this generous gift.

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Dr. Henry I. Shahon, Chief of the Medical Service and of the Allergy Department of the Veterans Administration Facility, West Roxbury 32, Massachusetts, has been promoted from Captain to Major. Doctor Shahon's book entitled "Compendio de Alergia Clínica," published by Hachette, Buenos Aires, has reached a large sale, and Major Shahon has completed an English edition.

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Recently, while in New York, Dr. Fred W. Wittich was presented with a check for \$350.00 for the Research Fund of the College, through a grateful patient. The names of the donors are as follows: Mr. Louis Levine, Mr. Julius Duberstein and Mr. and Mrs. Irving Solomon, all of New York City.

The College is deeply grateful for such additional contributions towards the establishment of two Research Fellowships, as announced in this issue.

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A very attractive 10-karat gold key, representing membership in the College, is now being manufactured for the members, including Associate Fellows and Fellows. A cut of the same will be mailed to all the members the first of the year. It is expected that some will be available by January 1 for those who wish to place their orders. The price is \$10, including mailing. Send orders to The American College of Allergists, 401 La Salle Medical Building, Minneapolis 2, Minnesota.

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The annual meeting of the Southwest Allergy Forum will be held at New Orleans Monday and Tuesday, April 9 and 10, 1945. Owing to war board restrictions in war zones, hotel reservations are available only to servicemen and families over week-

## NEWS ITEMS

ends. This has necessitated a change in the dates of the Forum meeting from Saturday and Sunday, as originally planned.

President Ralph Bowen urges that transportation and hotel reservations be made early. An excellent program is being arranged, a tentative outline of which will appear in the January-February issue of the *ANNALS*.

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Mrs. Ralph G. Mills, of Decatur, Illinois, writes that her late husband's practice and office equipment are available to a reputable physician and allergist who is looking for a location. Besides excellent facilities to practice medicine, Doctor Mills' allergy equipment is very complete, including much dependable material for testing and treatment. Among his numerous attainments, Doctor Mills was a botanist, and his oil extracts for patch testing are unusually complete. Any allergist returning from Service would step into a big vacancy here and render a great service to his patients when attempting to exemplify our late Fellow.

---

Complete sets of the instructional courses, presented at the first annual meeting of the College in Chicago, June 10 and 11, 1944, are no longer available. The second set of the printed instructional courses, presented at St. Louis, November 4 to 8, inclusive, are now available to all who desire them. These are much more comprehensive and inclusive. The mimeographed Manual of Allergy Laboratory and Diagnostic Procedures will also be printed and the sheets punched to fit a standard ring book so that revisions or additions may be made. The latter will be available very soon. A descriptive advertisement of the course appears in this issue. You are urged to place your order early.

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The Committee on Graduate and Undergraduate Education of the College is arranging a Speakers' Bureau. Printed forms of registration for this Bureau will be sent to the members. In this way, a list of speakers would be made available when the Committee plans the subject matter and leaders for the regional instructional courses and the presentation of papers at regional meetings of the College. It will also be useful when giving information concerning speakers to the program committees of county, state, district and other recognized medical societies. Anyone wishing to participate could list the subject he wishes to present, the investigative work done on the subject, and former and present teaching positions. On this registration blank could be listed films which any members wish to loan to the College for these regional instructional courses.

### SPECIAL ANNOUNCEMENT

Beginning with this number, an innovation is being made whereby the Spanish abstracts of all the scientific papers contained in each issue of the *ANNALS* will be published as a supplement to the *ANNALS*. By publishing the Spanish abstracts as a supplement, considerable space will be reserved within the *ANNALS* itself, and thereby a saving of paper will be accomplished, as the supplements containing the Spanish abstracts will be mailed to only those subscribers who desire them. If this policy proves popular with the Spanish readers, it is hoped that it may be continued.

# \* In Memoriam \*

## RALPH GARFIELD MILLS

Dr. Ralph Mills of Decatur, Illinois, died October 17, 1944, at the age of sixty-three years. He was born at Lincoln, Illinois. He received his A.B. in 1903 from Illinois, and his M.D., *cum laude*, in 1907, from Northwestern. He helped to build and was head of the Kennedy Hospital in Korea, 1908-1912; professor of pathology and bacteriology and head of the clinical laboratories and research department, Severance Union Medical College, Korea, 1913-1918. Later, in succession, he was in charge of the departments of pathology at Peking Union Medical College, China, and of the University of Colorado and the University of Minnesota Graduate School. He was a member of the American Association of Pathologists and Bacteriologists, Wisconsin Academy of Science, American Medical Association, American College of Allergists, Chicago Society of Allergy, Alpha Omega Alpha, Sigma Xi, and other organizations. He is survived by his wife, the former Mary E. Bumgarner, and a son and daughter.

Doctor Mills was a man of the highest integrity and was a friend of all of us. We shall miss him.

LEON UNGER.

### INSTRUCTIONAL COURSES AVAILABLE

Sets of the complete intensive instructional courses covering all phases of important allergic diseases, presented at St. Louis, November 4 to 8, inclusive, are now available. They include comprehensive outlines and lectures including tables, figures, diets, prescriptions, etc., with space for additional notes.

Subjects and authors are listed below:

- Dermatologic Allergy—Rudolf L. Baer, M.D., New York, N. Y.
- The Physiologic and Immunologic Aspects of Allergy (Illus.)—F. W. Wittich, M.D., Minneapolis, Minn.
- The Diagnosis and Treatment of Allergy of the Nose and Paranasal Sinuses—French K. Hansel, M.D., St. Louis, Mo.
- Some Neurologic and Psychologic Aspects of Allergy—Michael Zeller, M.D., Chicago, Ill.
- Food and Digestive Allergy (Illus.)—Herbert J. Rinkel, M.D., Kansas City, Mo.
- Allergy of the Central Nervous System—T. Wood Clarke, M.D., Utica, N. Y.
- Drug Allergy—Jonathan Forman, M.D., Columbus, Ohio.
- Pediatric Allergy—Ralph Bowen, M.D., Houston, Texas.
- Allergy Elimination Diets for Children, Albert V. Stoesser, M.D., Minneapolis, Minn.
- Mold Allergy (Illus.)—Homer E. Prince, M.D., Houston, Texas.
- Bronchial Asthma—Leon Unger, M.D., Chicago, Ill.
- Physical Allergy—Cecil M. Kohn, M.D., Kansas City, Mo.

The price of the complete set is \$3, and that of the Manual of Allergy Laboratory and Diagnostic Procedures is \$2. Please mail your check with your order.

AMERICAN COLLEGE OF ALLERGISTS  
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Minneapolis 2, Minnesota

# BOOK REVIEWS

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THE RECURRENCE OF REPEATED ERUPTIONS FOLLOWING VACCINE THERAPY (Les éruptions consécutives à l'emploi des vaccins médicamenteux). By Carlos Malbrán, M.D. 72 pages. Paris, France: Librairie Maloine, 1938.

In the preface of this book the author states that he was greatly impressed and encouraged by the excellent work of his teacher, Dr. M. Clement Simon of the Department of Venereal Diseases of Saint-Lazare Hospital in Paris, France.

He states that the skin has been considered for a long time as a symbol of internal reactions, or rather as a "mirror" of the various phenomena that take place in the organism. It is true, he adds, that these skin eruptions have been considered to be not so frequent, yet he believes that, at times, they are so outstanding and obstructing that they are serious enough to scare the patient, materially.

In the first chapter he discusses the different conceptions of the word "vaccine." He mentions the fact that there are many varieties of vaccines, namely: (1) vaccines that are composed of various bacteria killed in several ways, and suspended in physiological normal saline; (2) lipo-vaccines; (3) bouillon-vaccines, which appeared following the work of Pasteur; and (4) anatoxins, emphasized by Ramon.

The author feels that we should adhere to the interpretation of the term allergy as first conceived by Von Pirquet, namely "another reaction"; the reaction of the allergic subject is different than that of the new subject.

The word allergy comprises these three elements: (1) acquired hypersensitiveness, which gives a prematurity to the atypical or allergic reaction; (2) the existence of a relative immunity, which, even though incomplete, persists for a short time; and (3) every allergic state which is determined by the presence of a pre-existing specific inoculation.

In the second chapter he treats of the large and combined erythemas, febrile, that occurred following injections of Propidon, in a case of chronic cervicitis.

In the third chapter he discusses all other observations made by other workers, in this particular field, like Blum (P) and Bralez (J); Ferrabouc, Friess and Rolland (A); Gougerot (R), Barthélemy and Jean Will; Ledo (E); Milan (G); Périn and Huwart (P); Sézary, Dérôt and Guédé.

In the fourth chapter he deals with the pathogenic varieties of eruptions which follow vaccine therapy, both from external and internal causes.

He concludes with these remarks:

1. "We propose the following classification, etiopathogenic, for the consecutive eruptions following vaccinotherapy: A. *By an External Cause*, the vaccine itself; technical error, either in its preparation or in its dosage: (a) infectious eruption due to insufficient attenuation of the vaccine, (b) or an eruption of the toxic kind, arising from certain substances found in the vaccine itself, or due to large doses of this latter. B. *By an Internal Cause*: (a) contained in the individual himself, (b) caused by the awakening of latent bacteria, namely, biotrophic phenomena ("vaccinotropides"), following vaccinotherapy.

2. "We believe we have underlined the extreme rarity of eruptive accidents following series of vaccinotherapy, a method well used now. But if their frequency is small, its theoretic interest is important for the pathogenic study of certain skin diseases, and even for the general biologic problems.

3. "Our case of combined consecutive erythemas following injections of Propidon is an example of a biotrophic eruption ("vaccinotropide"). Whether it is a direct biotrophism, giving an atypical erysipelas to streptococci, or an erysipeloid to staphylococcus (Troisier), we do not know."

H.I.S.

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VOLUME 2

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# ANNALS of ALLERGY

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## *Abstracts*

DERMATOPATHIC LYMPHADENITIS IN INFANTILE ECZEMA. V. deP. Larkin, P. A. diS. Agnase, and M. N. Richter. J. Pedit., 24:442, (April) 1944.

While lymphadenopathy, which may be more or less generalized, involving even the mediastinal nodes, has been commonly noted in patients with eczema, the authors were unable to discover any reference to the histological appearance of the lymph nodes in infantile eczema. They observed that the degree of enlargement of the nodes is not necessarily related to the severity of the skin lesions but was most marked in those patients who fall into the group described by Hill as "atopic erythroderma." The characteristic histological picture was found to be replacement of the lymphatic tissue with proliferated reticulum cells, histiocytes and fibroblasts. Many of the histiocytes are lipophages and melanin and iron are present. Identical changes have been reported by Hurwitt under the name of "dermatophytic lymphadenitis" in lymph nodes removed from adults with chronic non-specific skin diseases characterized by pruritus. In the more severe cases the degree and generalized nature of the lymphadenopathy, together with the poor nutritional state of the infants and frequent high leukocyte counts suggested clinically a blood dyscrasia, or possibly Hodgkin's disease. The benign nature of the condition, however, is evident as the cases are observed over long periods of time, and the conclusions of those who have studied the condition, including Hurwitt and the authors, are that the adenopathy is of a benign reactive nature in response to the skin disease as an irritant.

J. G.

CLINICAL USE OF FLEA-ANTIGEN IN PATIENTS SENSITIVE TO FLEA BITES. B. C. McIvor and L. S. Cherney. Am. J. Trop. Med., 23:377, (May) 1943.

This is a report of the clinical trial of a new flea antigen which appears to be effective in desensitizing some individuals sensitive to flea bites. Among the cases reported was that of a three-year-old girl who suffered from asthmatic attacks with urticaria. The mother believed these to be due to flea bites. During the clinical trial of the flea antigen the child received a series of injections, each resulting in an asthmatic episode. She is said to have been greatly benefited by the treatments.

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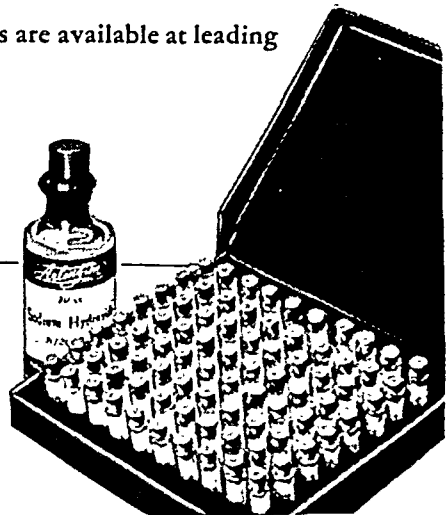
\*Turnbull, John A., Am. J. Digestive Dis., 11, 182, 1944.  
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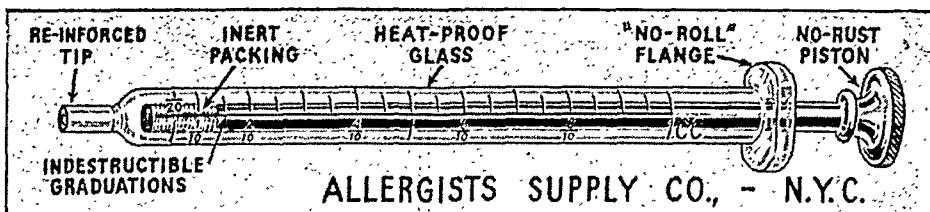
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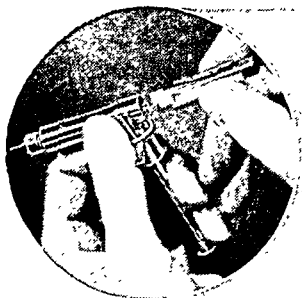
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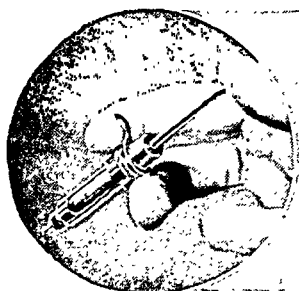
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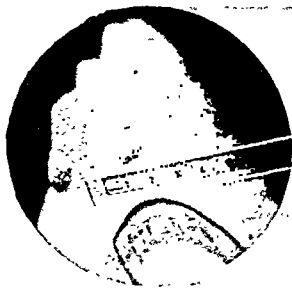
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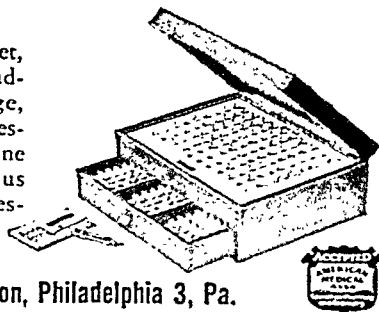
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